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TO WILLIAM TOWNSEND PORTER

When physiological science in America was searching for a suitable medium for the publication of the increasing output of its laboratories and when no solution of the vexing problem seemed at hand, William Townsend Porter proposed the establishment of a new journal, to be called THE AMERICAN JOURNAL OF PHYSIOLOGY, and offered to undertake its administration. The American Physiological Society contributed its name and its moral support; Professor Porter took upon himself the editorial and the financial burdens. These he has borne through sixteen years and through the JOURNAL'S first thirty-three volumes. From its inception his ideals were high. He believed that a meritorious discovery may fail of appreciation because of the faulty manner in which it is announced to the world, and that an editor may be of service to an investigator. He believed that a scientific journal, the organ of a national science, should be characterised by scientific merit, rhetorical excellence, the prompt publication of its contributions, and typography and illustration that are pleasing to the eye. These ideals he has maintained. A rigid pursuit of ideals by one individual frequently arouses in others lack of appreciation, criticism, and opposition; and these he has received without complaint. Time and effort and sacrifice of personal considerations have been given by him without stint. In now laying down these burdens and generously transferring to the American Physiological Society his interests he has given over a journal that has an assured position of merit among journals of physiology and that has been one of the chief agencies in the unification of American physiology. For his unselfish labors Professor Porter deserves the thanks of American physiologists, and as an expression of this gratitude they gladly dedicate to him this volume.

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STUDIES ON THE GROWTH OF MAN

1. The Pre- and Post-Natal Growth of Infants

T. BRAILSFORD ROBERTSON

From the Rudolph Spreckels Physiological Laboratory of the University of California

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INTRODUCTION

It is a well-known fact that the growth of an animal in weight or linear dimensions does not proceed with uniformly retarded or accelerated velocity from the moment of its inception until the period of its completion. On the contrary, growth will at first take place relatively slowly, then more rapidly and then

again more slowly, thus yielding an S-shaped curve of growth, and two or three of these sigmoid curves may be superimposed upon one another in the complete curve of growth of an animal. I have suggested that the period of growth covered by a *single* sigmoid curve should be termed a "growth cycle"[1] The extra-uterine growth of man consists of two growth cycles[2] and, as this article will show, a portion of a third, the inception of which occurs during the period of intra-uterine growth.

It has been shown by Read[3] that the intra-uterine growth of the guinea-pig consists of one whole growth-cycle and a portion of a second, birth occurring during the progress of the second growth-cycle. The point of junction of these cycles is a critical period in the growth of guinea-pigs. The juncture of the two cycles, at a period when growth is relatively slow, is not infrequently faulty, and as a consequence, it would appear, premature delivery of young, which are usually dead, occurs at this period much more frequently than at any other.

I have sought to ascertain whether or not a similar critical period occurs in the intra-uterine growth of infants. Through the courtesy of the Matron, Miss E. C. Sketheway, and of Dr. H. Gilbert, to whom I desire to express my very great indebtedness, I have had access to the extensive and admirably kept records of "The Queen's Home," a maternity hospital in Adelaide, South Australia.

2. The Pre-Natal Growth of South Australian Infants

I have sought to determine a portion of the pre-natal curve of growth from the weights of infants born at varying periods, somewhat prior to the normal period of gestation, and in order to obtain an estimate of the reliability of this method of procedure, I have also determined the weights of infants born somewhat

[1] T. Brailsford Robertson: Archiv f. Entwicklungsmechanik, 25 (1908), p. 581; 26 (1908), p. 108; 37 (1913), p. 497. Biologisches Zentralblatt, 30 (1910), p. 316; 33, (1913), p. 29. T. Brailsford Robertson and Hardolph Wasteneys, Archiv f. Entwicklungsmechanik, 37 (1913), p. 485.

[2] T. Brailsford Robertson: Arch. f. Entwicklungsmechanik, 25 (1908), p. 581.

[3] J. Marion Read: Arch. f. Entwicklungsmechanik, 35 (1912), p. 708.

later than the normal period. Since, as we shall see, this latter curve overlies and is identical with the continuation of the normal-curve of extra-uterine growth backwards to the time of birth, we are entitled to infer that the curve determined by the weights of prematurely delivered, but otherwise normal children, represents the further continuation of the normal curve of growth, backwards into the intra-uterine period.

The data employed were exclusively obtained from "The Queen's Home," and cover the years 1909–1913. Patients, upon admission to this hospital, pay a small and frequently nominal fee, the fee being in many cases adjusted to the income of the patient. The patient secures admission through the recommendation of the doctor in charge of the case. Unmarried mothers are not admitted. The mothers therefore belong to the laboring and lower artisan classes.

The mother is usually admitted at a period as near as possible to that of labor and then remains in the hospital for 14 days after the birth of the infant. The infant is weighed, without clothing, at birth, and again upon discharge (13 to 15 days). Recently the practice has been instituted of also weighing the infant at 1 week (6 to 8 days after birth). The balance employed is accurate to within $\frac{1}{2}$ ounce.

The period of gestation, when ascertainable, is indicated on the patient's record, the date recorded being that of the onset of the last menstruation. In tabulating the data, only those (about two-thirds of the actually recorded data) were employed in which this data was accurately indicated. All infants stated to be suffering at birth from syphilitic infections, deformities, etc., and all infants which died within one week after delivery are excluded. The infants delivered by mothers who were suffering at the time of delivery or prior thereto from zymotic disease or other pathological conditions of a serious nature are also excluded.

The following (Table 1) were the results obtained for males, all infants born between 275 and 285 days after the onset of the last menstruation being tabulated as having been born at 280 days, all between 285 and 295 days as having been born at 290

days, etc. Those born upon the limiting period separating two classes (e.g., 285 days) are included in both classes (e.g., 280 and 290).

A general tendency for increasing weight at birth to accompany increasing length of pregnancy is evident, but this becomes still more striking on *correcting* the above figures in the following way.

The *most probable* error in the estimation of the period of pregnancy is that of *one month*. Hence I assume that all periods

TABLE 1. MALES

(*Uncorrected Data*)

DAYS PREGNANCY	NUMBER OF INFANTS	AVERAGE WEIGHT IN OUNCES*
190	1	27
200	0	
210	1	54
220	0	
230	0	
240	1	123
250	2	117
260	22	119
270	38	121
280	79	127
290	78	130
300	16	139
310	9	138
320	3	123
330	1	152
340	0	

* I employ the ounce avoirdupois (1 ounce = 28.34 grammes) as the unit of weight because, in the first place, the weights of the infants were actually measured in terms of this unit and, in the second place, it is a unit of very convenient dimensions for this purpose.

of gestation which culminate in the delivery of infants weighing *less* than the uncorrected average for those born thirty days earlier, or *more* than the uncorrected average for those born thirty days later, are erroneously estimated and that the infants delivered in these cases should be excluded on account of this uncertainty in the estimation of the period of gestation. In this way we also probably exclude the majority of crypto-syphilitic infants born at the later periods of gestation.

The following (Table 2) are the *corrected* results for males, excluding those born before 260 or after 310 days as being two few in number and possibly representing pathological or erroneously estimated gestations.

The data for the 280-day infants were not corrected for three reasons. *Firstly*, because the 280-days group is the group nearest to the mean, the mean period of gestation for male infants (cf. below) being 282.5 days. *Secondly*, because the average weight of the 280-day infants (127 ounces) is the nearest to the average weight of *all* of the infants (127.3 ounces). *Thirdly*, because errors in the estimation of this period would obviously tend to cancel one another, being equally probably plus or minus.

TABLE 2. MALES
(*Corrected Data*)

DAYS PREGNANCY	NUMBER OF INFANTS	NUMBER OF INFANTS EXCLUDED	AVERAGE WEIGHT IN OUNCES
260	16	6	111
270	34	4	117
280	79	0	127
290	60	18	137
300	13	3	145
310	6	3	146

The following are the corresponding figures for females—

TABLE 3. FEMALES
(*Uncorrected Data*)

DAYS PREGNANCY	NUMBER OF INFANTS	AVERAGE WEIGHT IN OUNCES
190	1	39
200	2	59
210	0	
220	1	83
230	2	90
240	3	95
250	6	97
260	10	111
270	32	113
280	80	117
290	86	125
300	31	129
310	14	130
320	3	127
330	1	134
340	0	

TABLE 4. FEMALES

(*Corrected Data*)

DAYS PREGNANCY	NUMBER OF INFANTS	NUMBER OF INFANTS EXCLUDED	AVERAGE WEIGHT IN OUNCES
250	6	0	97
260	8	2	105
270	27	5	108
280	80	0	120
290	70	16	130
300	25	6	133*
310	11	3	138

* Excluding one infant weighing 184 ounces at birth which died within a fortnight of delivery.

As in the case of the male infants and for similar reasons, the data for the 280-day group are not corrected.

3. The Mean Period of Gestation for South Australian Infants

From the data recorded in Tables 2 and 4, it is possible to construct a curve displaying the intra-uterine growth of infants from the 250th day of gestation until the 310th day. In order to determine which portion of this curve represents *normally* intra-uterine growth and which portion represents normally extra-uterine growth it is necessary to determine with some exactitude the *mean period of gestation* for South Australian infants.

In attempting to determine this period, we might employ the average of all the different periods of gestation enumerated in Table 1 or 3, but in so doing, as we have seen, we should probably include some marked deviations from the true average, which represent departures from the mean period of gestation, which are not purely fortuitous and intrinsic in origin, but due to the intrusion of definite extrinsic variables such as pathological conditions of the mother or infant or large errors (1 month) in the estimation of the observed periods.

We might employ some arbitrary criteria for the exclusion of extreme deviations, as I have done in selecting the restricted

data enumerated in Tables 2 and 4. It should be noted, however, that the criterion employed in selecting these data is one which does not depend upon the magnitude of the period itself but upon the magnitude of another variable, namely the weight of the infant after delivery. For the purpose of obtaining the most probably correct estimates of the weights of infants delivered after varying periods of gestation, this procedure is justified, since by this means not only erroneously estimated periods of gestation are probably eliminated from the data, but also infants which, although born at correctly estimated periods, deviate so widely from the mean weight corresponding to those periods as to justify the suspicion that their development has been of an abnormal character. Abnormal development of the infant may frequently, but by no means necessarily, influence the length of the period of gestation. Consequently we should not be justified in excluding observed periods of gestation not differing too extremely from the mean on the sole ground of the super- or subnormal weight of the infant delivered.

We are therefore led to inquire what procedure we can employ, depending solely upon the magnitudes of the observed and apparently normal periods of gestation, which will enable us to exclude from the data enumerated in Tables 1 and 3 those of which the deviations from the mean are more probably due to extrinsic than to intrinsic variables, i.e., which are probably due to determinate but undetected large errors of estimation or pathological conditions.

Such a procedure, determined solely by the observed magnitude and not dependent upon any *a priori* considerations added thereto, is afforded by Chauvenet's criterion for the rejection of extreme variates,[4] which is widely employed in statistical investigations and physical measurements which involve a large number of determinations.[5] This criterion is evaluated in the following manner:

Referring to Table 1, we observe that out of a total of 251

[4] W. Chauvenet: A Manual of Spherical and Practical Astronomy, 5th ed. 1891, 2d vol., p. 558.

[5] Cf. C. B. Davenport: Statistical Methods, 2d ed., New York, 1904, p. 12.

male infants, one was born at 190 days, one at 210 days, one at 240 days, two were born at 250 days, and so forth, the average period of gestation for all of these infants being 281.8 days.

We now determine the deviation of each of the observed periods of gestation from the above average. Thus the deviation of the 190-day period is 91.8 days, that of the 330-day period is 48.2 days and so forth. Square each of these deviations, multiply each of these squares by the number of individuals displaying the deviation in question and add the products together. Thus Table 1 yields:

$91.8^2 \times 1 + 71.8^2 \times 1 + 41.8^2 \times 1 + 31.8^2 \times 2 + 21.8^2 \times 22 + 11.8^2 \times 38 + 1.8^2 \times 79 + 8.2^2 \times 78 + 18.2^2 \times 16 + 28.2^2 \times 9 + 38.2^2 \times 3 + 48.2^2 \times 1 = 74319.$

Divide this sum by the total number of infants (= 251) and take the square root of this quotient. The value thus obtained, 17.2, is the *standard deviation* of the period of gestation for male infants. The standard deviation is a measure of the variability of any quantity provided that quantity only varies accidentally, that is to say, in accordance with the laws of probability indifferently in excess and in defect of its mean value.[6]

When a series of magnitudes which deviate fortuitously from the mean are tabulated in classes, as we have tabulated periods of gestation in Tables 1 and 3, we find that those classes (in Table 1, the 280- and 290-day classes) which lie nearest in magnitude to the mean contain the greatest number of examples, i.e., exhibit the greatest "frequency." If we plot the frequencies of the classes vertically, employing their deviations from the mean as abscissae, we obtain, as is well-known, the "probability-curve."

$$y = \frac{n}{\sigma\sqrt{2\pi}} e^{-\frac{x^2}{2\sigma^2}}$$

in which n is the total number of "variates" (in this instance 251, the total number of infants), σ is the "standard deviation"

[6] Cf. C. B. Davenport: Statistical Methods, 2d ed., New York, 1904, p. 15. G. Udny Yule: An Introduction to the Theory of Statistics, 2d ed., London, 1912, chapter 8.

determined in the manner outlined above, y and x are the ordinate and abscissa respectively, and e is the base of the Napierian logarithms.

The general form of this curve is familiar. The majority of the variates lie close in magnitude to the mean, and therefore the greater part of the area enclosed between the curve and the axis of the abscissae lies close to the maximum ordinate, i.e., that expressing the number of variates exactly equal in magnitude to the mean. The curve slopes away upon either side of the mean, at first rapidly and then more slowly. The abscissa of the point of inflexion is σ, the standard deviation.

Assuming that the observed deviations of the experimental magnitude (in the particular instance in hand, the period of gestation) are for the most part purely fortuitous and therefore lie upon or near to the probability-curve, and having determined the "standard deviation" of the observed magnitudes, we can now proceed to determine which, if any, of the experimental deviations from the mean are probably not fortuitous in the following way:

Let x_1 be the magnitude of a given deviation, a expressed in terms of the standard deviation, so that $\frac{a}{\sigma} = x_1$, then the integral:

$$\varphi(\sigma x_1) = \frac{2}{\sigma\sqrt{2\pi}} \int_0^{\sigma x_1} e^{-\frac{x^2}{2\sigma^2}} dx$$

expresses the proportion of variates of which the deviation from the mean is *less* than a. If we multiply this by n, the total number of variates, we obtain $n\varphi(\sigma x_1)$ which is the actual number of variates of which the deviation from the mean is less than a. Substracting this from n we have:

$$n - n\varphi(\sigma x_1) = n[1 - \varphi(\sigma x_1)]$$

which is the number of deviations which must be expected to be *greater* than a. If now this quantity is less than $\frac{1}{2}$ it will follow that a deviation of magnitude a has a greater probability against it than for it, and we may infer that among a limited number of

purely fortuitous deviations it would not occur. Such a deviation from the mean we may therefore reject as being improbably fortuitous. The criterion for rejection is therefore obtained from the equation:

$$\varphi(\sigma x_1) = \frac{2n-1}{2n}$$

We have now to find the value of σx_1 which corresponds to an area of the probability-curve equaling $\frac{2n-1}{2n}$ where n is the total number of observations, in this instance 251. We can ascertain the value of x_1 by referring to tables of probability-integrals (such as, for example, Table IV in Davenport's "Statistical Methods" referred to above).

We have $\frac{2 \times 251 - 1}{2 \times 251} = 0.99801$. One-half of this area lies on either side of the mean, the tables of probability integrals give the values of x_1 corresponding to given areas on *one* side of the mean. We therefore divide the above area by 2, obtaining the area 0.49900. The table of probability-integrals shows that the value of x_1 which corresponds to this area is 3.09. Hence the limit of allowable deviation from the mean is given by:

$$a = \sigma x_1 = 17.2 \times 3.09 = 53.$$

This is therefore the maximum deviation from the mean period of gestation which may be expected to occur among 251 observations provided all of the observed deviations are fortuitous. Any period of gestation greater than $282 + 53 = 335$ days or less than $282 - 53 = 229$ days may therefore be eliminated from the observations as being probably attributable to the intrusion of extrinsic factors. Referring again to Table 1, we see that the 190- and 210-day periods may be rejected in computing the average magnitude of the period of gestation for males.

But in computing this maximum allowable deviation we began by assuming (in determining the "standard deviation") that the observed deviations from the mean were all fortuitous in origin. Nevertheless we have found that two of the observed

deviations were probably not fortuitous, but due to the intrusion of some extrinsic undetected variable into the system of varia' les which normally determine the length of the period of gestation. This renders a new application of Chauvenet's criterion necessary, in the carrying out of which we exclude these two observations and treat the remainder of the observed periods as the basis of a fresh estimate of the "standard deviation," the area of the probability-curve corresponding to the extreme allowable deviation and so forth, until we finally, by successive applications of Chauvenet's criterion, eliminate all the observations of which the deviations from the mean (corrected by the omission of these values) are too great to be merely fortuitous, and obtain a series of estimates of the period of gestation, all of which may legitimately be regarded as representing fortuitous deviations from a fixed average value.

Treating the data enumerated in Table 1 in this manner, we find that the *first* application of Chauvenet's criterion yields the limiting classes 229–335 days. The infants born at 190 and 210 days are therefore excluded. The *second* application of Chauvenet's criterion yields the limiting classes 242–322 days. The infants born at 240 and 330 days are therefore excluded. The *third* application of Chauvenet's criterion yields the limiting classes 243–321 days and leads to no further exclusions. We conclude therefore that with four exceptions, namely, the 190, 210, 240, and 330 day periods, all of the periods of gestation enumerated in Table 1 may be regarded as fortuitous departures from the true mean.

The number (N) of observed periods with the exception of those excluded by the above process is 247. The standard deviation (σ) for these periods is 12.7. The average of these periods is 282.5 days. The "probable error" of this estimate is given by $\pm 0.6745 \frac{\sigma}{\sqrt{N}} = \pm 0.55$, which means that the chances are even (1 to 1) that the true value of the mean period of gestation for males lies between 281.95 and 283.05 days.[7]

[7] Cf. C. B. Davenport: loc. cit. p. 15.

Applying the same methods of computation to the data for female infants enumerated in Table 3 we find that the *first* application of Chauvenet's criterion yields the limiting classes 228–338 days. The infants born at 190, 200, and 220 days are therefore excluded. The *second* application of Chauvenet's criterion yields the limiting classes 241–329 days. The infants born at 330 days are therefore excluded. The *third* application of Chauvenet's criterion yields the limiting classes 241–327 days and leads to no further exclusions. We conclude therefore that with 7 exceptions, comprising the 190, 200, 220, and 330 day periods, all of the periods of gestation enumerated in Table 3 may be regarded as fortuitous departures from the true mean.

The number (N) of observed periods with the exception of those excluded by the above process is 264. The standard deviation (σ) for these periods is 13.8. The average of these periods is 284.5 days. The "probable error" of this estimate is $\pm$ 0.57. The chances are therefore even that the true period of gestation for female infants lies between 283.93 and 285.07 days.

From these results it appears that the mean period of gestation for female infants is longer than that for male infants. The probability of the truth of this conclusion is the inverse of the probability that either of the above estimates, namely, that of the period of gestation for male infants or that of the period of gestation for female infants, differs from the true mean by four times the "probable error" of the estimate of either mean, which is the extent of the divergency of the two estimates. Hence the probability of the truth of the conclusion that the period of gestation is longer for female infants than for male infants is 142 to 1.[8]

It should be noted that the ordinary method of estimating the probable period of gestation, namely, that of adding seven days to the date of the onset of the last menstruation and subtracting three calendar months from that date in the following year, yields periods which vary in length between 280 and 283 days.

[8] Cf. C. B. Davenport, loc. cit,, p. 14.

4. The Mean Weight at Delivery of Normally Delivered South Australian Infants

We have seen that with the exclusion of a small number of extreme and probably pathological or erroneously estimated deviations, the mean period of gestation for South Australian male infants is 282.5 days, while that for female infants is 284.5 days. We may assume, therefore, that with the same exclusions the mean weight of the infants at birth represents their weight at this period of their development, namely, at 282.5 days for males and 284.5 days for females.

The average weight at birth of all of the male infants, exclusive of those born at periods of gestation which are rejected by Chauvenet's criterion, is 127.3 ounces. On referring to Table 2, it will be seen that this lies between the weight of male infants born at 280 days and that of male infants born at 290 days, considerably closer to the weight of the former than that of the latter group.

The average weight at birth of all of the female infants, exclusive of those born at periods of gestation which are rejected by Chauvenet's criterion, is 121.2 ounces. On referring to Table 4, it will be seen that this lies between the weight of female infants born at 280 days and that of female infants born at 290 days, again considerably closer to the weight of the former than to that of the latter group.

The "standard deviation" of the weight at birth is 18.2 ounces for male and 17.6 ounces for female infants. The standard deviation is a measure of the *absolute variability* of a quantity. The *percentage variability* is yielded by the ratio of the standard deviation to the mean multiplied by one hundred.[9] Thus the percentage variability of the weight of South Australian male infants at birth is

$$\frac{18.2}{127.3} \times 100 = 14.3 \text{ per cent}$$

[9] Karl Pearson: Phil. Trans. Roy. Soc. London, 187 A, (1896), p. 253. Cf. C. B. Davenport, loc. cit., p. 16.

while that of the weight of South Australian female infants at birth is

$$\frac{17.6}{121.2} \times 100 = 14.5 \text{ per cent}$$

These figures mean that out of any group of normally delivered male infants selected by chance 68.27 per cent or approximately two-thirds will weigh within 14.3 per cent of the mean weight, while out of any group of normally delivered female infants selected by chance two-thirds will weigh within 14.5 per cent of the mean weight.

The British Anthropometric Committee[10] reports that the average weight at birth of 451 male infants born in London and Edinburgh is 113.6 ounces, while that of 466 female infants is 110.4 ounces. According to Pearson,[11] the mean weight at birth of 1000 male infants born in London (Lambeth Lying-in Hospital) is 116.8 ounces with a variability of 15.7 per cent, while that of 1000 female infants is 113.2 ounces, with a variability of 14.2 per cent. Through the courtesy of Dr. Smallwood Savage and of Dr. Elsie M. Humpherson, to whom I desire to express my great indebtedness, I have been furnished with the weights of one hundred male and one hundred female infants at birth, chosen without selection from the records of normal full-term deliveries in the Maternity Hospital of Birmingham, England. From these data I find that the average weight of male infants at birth in Birmingham is 114.9 ounces with a variability of 13.2 per cent, while the average weight of female infants at birth is 113.5 ounces, with a variability of 12.5 per cent.

From these figures, a striking fact emerges, namely, that South Australian infants weigh from 8 to 10 ounces more at birth than infants born in Great Britain. This fact is remarkable because, according to an article on the "People of Australia," contributed by G. H. Knibbs, Commonwealth Statistician, to the *Federal Handbook on Australia* issued by the British Association for the Advancement of Science in 1914, "The Australian

[10] Report of the British Assoc. for the Adv. of Science, 1883, p. 285.

[11] Karl Pearson: Proc. Roy. Soc. London, 66 (1899), p. 23.

people, with regard to racial constitution, are virtually British, as the following figures from the last census show, and it may be added that the descendants of other European races disclose but small differentiation from their fellow citizens of British origin. The percentages of the principle races represented are as follows:

"Australian born 82.90 per cent; natives of United Kingdom 13.37; of New Zealand 0.72; of Germany 0.75; of China 0.47; of Scandinavia 0.33; of all other places 1.46; that is to say, at the date of the census, 1911, no less than 97 per cent had been born either in Australasia or in the United Kingdom.

"The evolution of the Australian people, therefore, may be regarded as that of the British people under changed climatic, social, and economic conditions."

The results observed cannot be due to any racial selection among the immigrants from the British Isles who have given rise to the population of Australia, for in the first place there is no evidence that such selection has occurred to any greater extent than it has for example, in London, of which city the very great increase in population during the past century has been contributed by all parts of the British Isles, and in the second place there is no evidence of the existence of a race in the British Isles which is in any noteworthy degree superior in physical dimensions to the average inhabitant of England.[12] We can only infer, therefore, that the superior weight of the Australian infant at birth is attributable to the factors enumerated by the Commonwealth Statistician, namely, the change in climatic, social, and economic conditions. The climate is much less rigorous than that of England, food is cheaper in proportion to income or, when of a like price, better in quality, and the social and economic conditions are so far an improvement upon those prevailing in England that whereas women of the laboring and lower artisan classes in England have frequently to supplement the family income by their own exertions, those of the corresponding classes in Australia as a rule confine their physical activities to the management of their households and families, a condition of

[12] Cf. Brit. Anthropometric Committee's report, Report of the British Assoc. for the Adv. of Science, 1883, p. 253.

affairs which, quite apart from the possible direct effects of physical labor upon the mother, must have important indirect effects in ameliorating the nutritional and hygienic conditions within the household. These conditions may be conceived to have an appreciable pre-natal effect upon the growth of children since Pinard has shown that the rest and improved nutrition of hospital life causes a notable increase in the average weight of infants delivered by working mothers who spend a part or a whole of the period of pregnancy in a lying-in hospital[13] and Prochownik has shown[14] that the size of a child at delivery may be reduced by restricting the diet of the mother.

Not only are South Australian infants heavier at birth than infants born in the British Isles, but they are also from 5 to 6 ounces heavier at birth than infants of English descent born in the Eastern United States, for according to Bowditch[15] the average weight of Anglo-American male infants at birth is 120.8 ounces, that of Anglo-American female infants 115.7 ounces. The Anglo-American infant is therefore intermediate as regards weight at birth between the Australian infant and the British infant. This very clearly corresponds with the character of the social and economic conditions prevailing in these three countries. It would appear, therefore, that the mean weight of infants of the same race at birth is a very sensitive criterion of the social and economic environment in which they are born.

It will be observed that the *variability* of the weight of South Australian infants at birth is very nearly the same as that of infants born in London or in Birmingham, with this difference, that whereas Pearson finds for London infants that the variability of males is greater than that of females, and the figures above cited for Birmingham infants exhibit a somewhat smaller excess of variability in males, South Australian male infants would appear not to be more variable at birth than females.

[13] Cited after G. Newman: Infant Mortality, London, 1906, p. 81.

[14] Cited after G. Newman: loc. cit., p. 84.

[15] H. P. Bowditch: Eighth Annual Report, State Board of Health, Massachusetts, 1877. Cited after Report of the British Assn. for the Adv. of Science, 1879, p. 200.

The various data concerning the weights of British infants at birth in different localities are exhibited in tabular form below:

TABLE 5

PLACE OF BIRTH	SEX	NUMBER WEIGHED	MEAN WEIGHT AT BIRTH IN OUNCES	VARIABILITY
				per cent
London and Edinburgh (British Anthropometric Committee)	Male	451	113.6	
	Female	466	110.4	
London (Pearson)	Male	1000	116.8	15.7
	Female	1000	113.2	14.2
Birmingham	Male	100	114.9	13.2
	Female	100	113.5	12.5
Eastern United States (Bowditch)	Male	100	120.8	
	Female	100	115.7	
Adelaide, South Australia	Male	247	127.3	14.3
	Female	264	121.2	14.5

5. The Post-Natal Growth of South Australian Infants

The object of this investigation being primarily to determine the relationship of the curve of pre-natal growth, determined from the weight of normal infants somewhat prematurely delivered, to the curve of post-natal growth, it was necessary for the attainment of this object to determine the post-natal curve of growth for South Australian infants of the class (laboring and lower artisan) from which the data for weight at birth were obtained. These data I was enabled to obtain through the kindness of Miss A. Hornabrook (Hon. Secretary of the Adelaide School for Mothers), Miss H. A. Stirling (member of the Committee), and Nurse Clara Webb (Superintendent) by whom the data in the possession of the "Adelaide School for Mothers" were placed at my disposal and to whom I desire to express my very great indebtedness.

The "Adelaide School for Mothers Institute" offers instruction to mothers regarding the feeding and care of their infants at a nominal charge. At frequent intervals the Registrar of Births for the State of South Australia reports to the Institute the births which have occurred in its neighborhood, and a nurse in the em-

ploy of the Institute then calls upon those mothers who, being known to be more or less needy in circumstances, are likely to have insufficient medical advice, and proffers them the services of the Institute. The infants are voluntarily brought to the Institute by the mothers upon certain days when the nurse is in attendance. The infants, without clothing, are weighed by the nurse and the weight and date are noted upon a card bearing the infant's name. Other data of importance, such as the nature of the infant's food, illnesses, etc., are also noted upon the card and these records are kept on file.

The infants which are brought to the Institute therefore belong to the laboring and lower artisan classes. They include a large proportion of sickly infants, since mothers who appreciate the benefits accruing from the advice and help they have received advise friends, and especially friends with ailing infants, to bring their children to the Institute.

The following data (Tables 6 to 9) are computed from the records of this Institute accumulated in the years 1910–1913 up to but not including those of July 21, 1913. All data concerning infants suffering from definite ailments or requiring medical attendance are excluded. When infants which were otherwise normal contracted zymotic diseases, such as mumps, measles, etc., the weights recorded prior to the decrease in weight immediately preceding or accompanying recognition of the disease are included in the data, subsequent weighings being rejected. In cases where no loss of weight had occurred at the time of recognition of the disease, weights preceding recognition of the disease were included, weighings subsequent to this being excluded. Data concerning twins were excluded.

The data are obtained from repeated weighings at irregular intervals of 159 "normal" infants, classified as follows:

Breast-fed males	63	Total males	90
Bottle-fed males	27		
Breast-fed females	43	Total females	69
Bottle-fed females	26		

The "breast-fed" classes include all infants stated to have been breast-fed, irrespective of the period during which they were so

fed. Infants are considered to have been bottle-fed when there is no record of breast-feeding upon their cards. Hence some of the bottle-fed infants which were first brought to the School for Mothers during the latter months of their first year were probably breast-fed during some period prior to the date when they first came under observation.

The weights are grouped into periods of 30 days. All weights recorded between the 15th and 45th days succeeding births are regarded as weights at 30 days and so forth. When more than one weighing was recorded for one infant in one such 30-day period, the different weighings are averaged, fractions of an ounce less than $\frac{1}{2}$ being regarded as zero, while fractions of an ounce equal to or greater than $\frac{1}{2}$ are regarded as 1 ounce. Weighings falling exactly upon the limiting date separating two periods (e.g., exactly upon the 45th day) are placed in both classes (e.g., the 30-day and the 60-day classes).

The balance employed for weighing was accurate to 1 ounce. The following are the summarized data (Tables 6 and 7).

The superiority of the breast-fed child, which has so frequently been commented upon by numerous observers, is here again strikingly revealed. On comparing the above data with similar data for English children, such as Sir George Newman's standard

TABLE 6. MALES

AGE IN MONTHS OF 30 DAYS	BREAST-FED		BOTTLE-FED	
	No. infants weighed	Average weight in ounces	No. infants weighed	Average weight in ounces
1	20	155	5	117
2	27	187	14	141
3	30	206	11	169
4	26	224	9	193
5	24	254	9	226
6	23	270	8	242
7	25	287	3	267
8	22	300	3	329
9	20	311	8	280
10	11	326	6	298
11	10	333	7	322
12	6	330	5	335

TABLE 7. FEMALES

AGE IN MONTHS OF 30 DAYS	BREAST-FED		BOTTLE-FED	
	No. infants weighed	Average weight in ounces	No. infants weighed	Average weight in ounces
1	12	153	3	120
2	26	168	11	137
3	23	188	10	156
4	20	209	11	179
5	21	224	10	184
6	17	253	11	198
7	15	263	8	212
8	9	270	8	239
9	8	300	6	259
10	6	315	7	252
11	6	335	7	265
12	5	345	7	288

growth-curve,[16] it is evident that the superiority of the Australian child at birth is maintained in varying proportion throughout the first year of post-natal life. This remains the case even when allowance has been made for the fact, which I will show in a subsequent publication, that Sir George Newman's standard is somewhat too low.

6. The Formulation of the Relationship Between Age and Weight in the Post-Natal Curve of Growth for South Australian Infants

In seeking to determine whether or to what extent the curve of pre-natal growth determined from the weights of prematurely delivered infants represents the continuation of the post-natal curve of growth, we might proceed by simply drawing a curve through the points determined upon the post-natal curve, and continuing it backwards from birth estimate approximately the degree of resemblance of this graphically constructed curve to the pre-natal curve of growth. Such a method would yield only a very approximate and indefinite comparison, however.

[16] G. Newman: Infant Mortality, London, 1906. Cf. also H. W. Pooler, Sixth Annual Report of the Birmingham Infants' Health Society, 1913.

A much more reliable comparison may be made by fitting some algebraic interpolation-formula to the post-natal curve. Such a formula will yield, by inserting in it varying values of the time coördinate, not only weights interpolated between those ascertained by measurement, but also values exterpolated therefrom and continuing the curve in either direction (i.e., pre-natally or subsequently to the twelfth month of post-natal growth). Such continuations may be relied upon, if the interpolation-curve be so chosen as to fit the observations closely, to represent the true continuation of the curve of growth, provided only that the exterpolation is not too extreme, that is, provided we do not seek to extend the observation-curve too far.

A large number of well-known interpolation-formulae, which are frequently employed in physical and statistical investigations are at our disposal for this purpose. We might, for example, express the weight x of an infant in terms of ascending powers of t, its age, thus:

$$x = a + bt + ct^2 + dt^3 + \ldots\ldots$$

where a, b, c, d, etc., are constants[17] and it would only be a question, as in other physical measurements, of employing a sufficient number of terms and constants to obtain an equation expressing to any desired degree of accuracy the observed magnitudes.

I have, however, shown in previous communications[18] that the relationship between weight and time for any single growth-cycle is the same as that which subsists between the extent of transformation and the time in an autocatalysed chemical reaction, that is to say, a reaction one of the products of which accelerates it. The formula expressing this relationship is:

$$\log \frac{x}{A - x} = K\,(t - t_1)$$

[17] C. Henry et L. Bastien: Comptes rendus de l'Association Francaise pour l'avancement des Sciences, 1904. P. Enriques, Biologisches Centralbl., 29 (1909), p. 331. T. Brailsford Robertson, Ibid, 30 (1910) p. 316.

[18] T. Brailsford Robertson: Arch. f. Entwicklungsmechanik, 25 (1908), p. 581; 26 (1908), p. 108.

where A is a constant (= the maximum weight attained by the particular growth-cycle under consideration), t_1 is a constant (= time at which the growth-cycle is half-completed), K is a constant, and x and t are the weight and time respectively.

We may therefore employ this formula as a means of exterpolating from (continuing) the observed curve of growth in preference to any of the other interpolation-curves at our disposal. It should be noted, however, that the results of the exterpolation are quite independent of any particular deductions concerning the actual nature of the growth-process. I have concluded from the form of the curve representing a growth-cycle and from other data[19] that the process of growth represents the progress of a self-accelerated chemical reaction. Should this conclusion prove invalid, however, the conclusions reached by employing the curve of autocatalysis as a means of exterpolating from the observed curve of growth will not be invalidated, for the form of the exterpolated curve, for moderate exterpolations would be substantially the same whatever the form of the algebraic expression employed to represent the observed data. On the other hand, the convenient form of the algebraic expression for the curve of autocatalysis and the small number of constants involved present obvious advantages over more unwieldy formulae which might yield an equally faithful reproduction of the observed data.

We shall only employ, for the purpose of exterpolation, the data for breast-fed infants, since these may safely be presumed to be the most "normal" data available.

In fitting the curve of autocatalysis to the results for breast-fed males (Table 6) we proceed as follows[20] to obtain approximate values of A, K and t_1, in the equation

$$\log \frac{x}{A - x} = K\,(t - t_1).$$

Representing graphically in the usual manner the curve of

[19] T. Brailsford Robertson: loc. cit.; also Arch. f. Entwicklungsmech., 37 (1913), p. 497.

[20] T. Brailsford Robertson: Arch. f. Entwicklungsmech., 25 (1908), p. 581.

growth of South Australian infants during their first post-natal year it is at once evident that the end of the first year represents approximately the conclusion of a sigmoid curve. In this region the growth-curve for man enters, as is well-known, upon a "plateau" or period of relatively slow growth such as characterises the conclusion of a growth-cycle. The value of A for this cycle is therefore, probably, greater, but not very much greater than the value of x (= weight in ounces) at 12 months. Hence, as a first approximation, we may take the value of A for South Australian males (cf. Table 6) as 334 ounces. The value of t_1 is the value of t when $x = \frac{1}{2}A = 167$; this is the point of inflexion of the curve, when from being convex it becomes concave to the time-axis. We observe (Table 6) that at one month after birth $x = 155$ ounces, while at two months after birth $x = 187$ ounces. The point of inflexion occurs at a value of t, therefore, lying between one and two months. Let y be the fraction of a month in excess of one at which the point of inflexion occurs. Then to a first approximation:

$$y = \frac{167 - 155}{187 - 155} = 0.375$$

Hence t_1 equals, approximately, 1.375 months, reckoning from birth.

The value of x *at birth* ($t = 0$) is probably the most accurate, since 247 infants were weighed in determining this value for males. Putting the above values of A and t_1 in the equation $\log_{10} \frac{x}{A - x} = K\,(t - t_1)$, and putting $t = 0$ and $x = 127$ (= weight at birth) we obtain $K = 0.154$.

The equation $\log_{10} \frac{x}{A - x} = K\,(t - t_1)$ may be written

$1/K \log_{10} \frac{x}{A - x} + t_1 = t$. Inserting the above approximate values of the constants, we obtain:

$$6.5 \log_{10} \frac{x}{334 - x} + 1.375 = t.$$

in which t is the time which has elapsed since birth, and x is the weight of the infant.

We now proceed to correct these arbitrary and approximate values of the constants from all of the observations by the method of least squares as follows:[21]

Designating the arbitrarily chosen constants by the symbols a, b, and c, so that $a \log_{10} \frac{x}{b-x} + c = t$, let the *most probable* values of these constants be designated, respectively, $1/K$, A and t_1.

Then
$$\begin{aligned} 1/K &= a + \alpha = 6.5 + \alpha \\ A &= b + \beta = 334 + \beta \\ t_1 &= c + \gamma = 1.375 + \gamma \end{aligned}$$

where α, β and γ are small corrections the *most probable* values of which are now to be determined from all of the observations cited in Table 6.

Expanding the function:

$$\varphi = 1/K \log \frac{x}{A-x} + t_1 - t.$$

by Taylor's Theorem, inserting the above values for $1/K\,(=a+\alpha)$, $A\,(=b+\beta)$, and $t_1\,(=c+\gamma)$ we obtain:

$$\varphi = a \log \frac{x}{b-x} + c - t + \frac{d\varphi}{d\,(1/K)}\alpha + \frac{d\varphi}{dA}\beta + \frac{d\varphi}{dt_1}\gamma = 0$$

Inserting the known values of a, b, and c, and the experimental values of x and t, we obtain a series of values of

$a \log_{10} \frac{x}{b-x} + c - t$ which we may designate by the symbol $-\theta$.

$$\text{Hence: } \frac{d\varphi}{d\,(\frac{1}{K})}\alpha + \frac{d\varphi}{dA}\beta + \frac{d\varphi}{dt_1}\gamma = \theta \quad . \quad . \quad . \quad . \quad (1)$$

From the form of the equation:

$$\varphi = 1/K \log_{10} \frac{x}{A-x} + t_1 - t$$

[21] Cf. M. Merriman, A Text-book on the Method of Least Squares, 8th ed., New York, 1910, p. 200.

it is evident that:

$$\frac{d\varphi}{d\,1/K} = \log_{10}\frac{x}{A-x}$$

to a very close approximation this may be written:

$$\frac{d\varphi}{d\,1/K} = \log_{10}\frac{x}{b-x} = \log_{10}\frac{x}{334-x}$$

Similarly:[22]

$$\frac{d\varphi}{dA} = \frac{-0.4343}{K\,(A-x)} = \frac{-6.5\times 0.4343}{344-x}$$

$$\frac{d\varphi}{dt_1} = 1$$

Computing the values of $\frac{d\varphi}{d\,1/K}$, $\frac{d\varphi}{dA}$, $\frac{d\varphi}{dt_1}$ and θ for each of the experimental values of x and t and inserting these values in equation (1) we obtain the following series of *observation equations*:

TABLE 8. MALES

AGE OF INFANT IN MONTHS	OBSERVATION—EQUATIONS	"WEIGHTS"
0	$-0.212\alpha - 0.0136\beta + \gamma = +0.003$	247
1	$-0.063\alpha - 0.0158\beta + \gamma = +0.035$	20
2	$+0.105\alpha - 0.0192\beta + \gamma = -0.058$	27
3	$+0.207\alpha - 0.0221\beta + \gamma = +0.279$	30
4	$+0.309\alpha - 0.0257\beta + \gamma = +0.616$	26
5	$+0.502\alpha - 0.0354\beta + \gamma = +0.362$	24
6	$+0.626\alpha - 0.0441\beta + \gamma = +0.556$	23
7	$+0.786\alpha - 0.0603\beta + \gamma = +0.516$	25
8	$+0.945\alpha - 0.0830\beta + \gamma = +0.482$	22
9	$+1.131\alpha - 0.1230\beta + \gamma = +0.273$	20
10	$+1.609\alpha - 0.3540\beta + \gamma = -1.834$	0
11	$+2.523\alpha - 2.8230\beta + \gamma = -6.775$	0
12	$+1.917\alpha - 0.7080\beta + \gamma = -1.836$	0

All of these observation-equations are not of equal value, since the first, that for birth, was derived from the determination of the mean weight of 247 infants, while the second, namely, that for one month, was derived from measurements made upon only 20 infants. Hence, in order to ascribe to each observation

[22] Since $\log_{10}\frac{x}{A-x} = 0.4343\,\mathrm{Log}_{\mathrm{nat}}\frac{x}{A-x}$

its just value the equations must be *weighted* in proportion to the number of infants observed. This we do by multiplying every term in each equation by the number of infants observed.[23] I have, however, weighted the observations for 10, 11 and 12 months *zero*. This is for three reasons, namely: *First*, the small number of observations at each of these ages, were this the only ground for suspecting these observations it would be adequately provided for by weighting in proportion to that number, but there are also the following grounds for rejecting the data in estimating the true form of the curve of growth for the infantile growth-cycle. *Secondly*, at this part of the curve of growth the *second* extrauterine growth cycle (that which reaches its maximum velocity at 5.5 years[24] may be beginning to contribute an appreciable proportion to the growth of the infants and thus modify the form of the first growth cycle. *Thirdly*, small errors in the determination of x at this point lead to large errors in the estimation of $\frac{d\varphi}{dA}$ and therefore to large errors in the multipliers of β in the observation-equations which would result, if these equations were "weighted" in the same manner as the others, in giving slight errors in the determinations of mean weight at 10 to 12 months an undue effect in determining the most probable values of α, β and γ.

Proceeding in this way we obtain the following weighted observation-equations (Table 9).

TABLE 9. MALES.

AGE OF INFANT IN MONTHS	WEIGHTED OBSERVATION-EQUATIONS X Y Z θ
0	$-52.364\alpha - 3.360\beta + 247\gamma = + 0.741$
1	$- 1.260\alpha - 0.316\beta + 20\gamma = + 0.700$
2	$+ 2.835\alpha - 0.520\beta + 27\gamma = - 1.566$
3	$+ 6.210\alpha - 0.660\beta + 30\gamma = + 8.370$
4	$+ 8.034\alpha - 0.670\beta + 26\gamma = + 16.016$
5	$+12.048\alpha - 0.848\beta + 24\gamma = + 8.688$
6	$+14.398\alpha - 1.180\beta + 23\gamma = + 12.788$
7	$+19.650\alpha - 1.505\beta + 25\gamma = + 12.900$
8	$+20.790\alpha - 1.830\beta + 22\gamma = + 10.604$
9	$+22.620\alpha - 2.460\beta + 20\gamma = + 5.460$

[23] Cf. M. Merriman: loc. cit., p. 36.

[24] Cf. T. Brailsford Robertson: Arch. f. Entwicklungsmech., 25 (1908), p. 581.

Calling the multipliers of α, β and γ x, y and z respectively, the "Normal-Equations" derivable from the above observation-equations are:

$$\alpha\,\Sigma x^2 + \beta\,\Sigma xy + \gamma\,\Sigma xz = \Sigma x\,\theta \ldots\ldots\ldots\ldots\ldots \text{I}$$
$$\alpha\,\Sigma xy + \beta\,\Sigma y^2 + \gamma\,\Sigma zy = \Sigma y\,\theta \ldots\ldots\ldots\ldots\ldots \text{II}$$
$$\alpha\,\Sigma xz + \beta\,\Sigma yz + \gamma\,\Sigma z^2 = \Sigma z\,\theta \ldots\ldots\ldots\ldots\ldots \text{III}$$

Computing the corresponding numerical values we obtain the equations:

$$4541.00\alpha + 16.82\beta - 10470\gamma = +1023.0 \ldots\ldots\ldots \text{I}$$
$$16.82\alpha + 25.92\beta - 1058\gamma = - 91.5 \ldots\ldots\ldots \text{II}$$
$$10470.00\alpha - 1058.00\beta + 66330\gamma = +1990.0 \ldots\ldots\ldots \text{III}$$

Solving, we obtain:

$$\alpha = +0.853$$
$$\beta = +7.47$$
$$\gamma = +0.284$$

Hence the most probable values of:

$$1/\mathrm{K} = \mathrm{a} + \alpha = 6.5 + 0.85 = 7.35$$
$$A = b + \beta = 334 + 7.47 = 341.5$$
$$t_1 = c + \gamma = 1.375 + 0.284 = 1.66$$

Hence the equation to the curve of growth for the first nine months of the extra-uterine life of South Australian males is found to be:

$$\log_{10} \frac{x}{341.5 - x} = 0.136\,(t - 1.66) \ldots\ldots\ldots\ldots (2)$$

t being reckoned from the time of birth and x in ounces.

In the following table (Table 10) the observed weights at the various ages are compared with those calculated from the above formula.

The agreement between the observed and calculated values is obviously excellent. From the values of the deviations enumerated in the fourth column we can calculate the probable deviation of any observed value from its calculated value, employing the formula

$$\text{"Probable deviation"} = 0.6745 \sqrt{\frac{\Sigma p \Delta^2}{\text{Total number of observations}}}$$

TABLE 10. MALES

AGE OF INFANT IN MONTHS	WEIGHT IN OUNCES		Δ=DEVIATION FROM CALCULATED VALUE
	Observed	Calculated	
0	197	127	±0
1	155	156	−1
2	187	180	+7
3	206	206	±0
4	224	230	−6
5	254	254	±0
6	270	273	−3
7	287	288	−1
8	300	301	−1
9	311	311	±0
10	326	319	+7
11	333	325	+8
12	330	330	±0

where p is the "weight" of a single observation and Δ the observed deviation.[25] In this way we find that the "probable deviation" of an observed from a calculated value, as indicated by the comparison in Table 10, is ± 1.5, which means that the agreement between theory and observation is such that as many observed values will be found to depart from the calculated value by *less* than 1.5 ounces as will be found to depart from the calculated value by *more* than 1.5 ounces. The corresponding computations for female infants follow (Tables 11 and 12), employing the approximate equation $8.0 \log \frac{x}{336 - x} + 2 = t$

TABLE 11. FEMALES

AGE OF INFANT IN MONTHS	OBSERVATION-EQUATION	"WEIGHTS"
0	$-0.250\alpha - 0.0162\beta + \gamma = \pm 0.000$	264
1	$-0.077\alpha - 0.0190\beta + \gamma = -0.384$	12
2	$\pm 0.000\alpha - 0.0207\beta + \gamma = \pm 0.000$	26
3	$+0.104\alpha - 0.0235\beta + \gamma = +0.168$	23
4	$+0.216\alpha - 0.0274\beta + \gamma = +0.272$	20
5	$+0.301\alpha - 0.0310\beta + \gamma = +0.592$	21
6	$+0.484\alpha - 0.0419\beta + \gamma = +0.128$	17
7	$+0.556\alpha - 0.0476\beta + \gamma = +0.552$	15
8	$+0.612\alpha - 0.0526\beta + \gamma = +1.104$	9
9	$+0.922\alpha - 0.0965\beta + \gamma = -0.376$	8

[25] Cf. M. Merriman, loc. cit., p. 82.

TABLE 12. FEMALES

AGE OF INFANT IN MONTHS	WEIGHTED OBSERVATION-EQUATIONS X Y Z θ
0	$-66.00\alpha - 4.277\beta + 264\gamma = \pm 0.00$
1	$- 0.94\alpha - 0.228\beta + 12\gamma = - 4.51$
2	$\pm 0.00\alpha - 0.538\beta + 26\gamma = \pm 0.00$
3	$+ 2.39\alpha - 0.541\beta + 23\gamma = + 3.86$
4	$+ 4.32\alpha - 0.548\beta + 20\gamma = + 5.44$
5	$+ 6.32\alpha - 0.651\beta + 21\gamma = +12.43$
6	$+ 8.25\alpha - 0.712\beta + 17\gamma = + 2.04$
7	$+ 8.34\alpha - 0.714\beta + 15\gamma = + 8.28$
8	$+ 5.51\alpha - 0.473\beta + 9\gamma = + 9.94$
9	$+ 7.37\alpha - 0.772\beta + 8\gamma = - 2.94$

From these observation-equations we obtain the following normal-equations:

$$4643.0\alpha + 254.50\beta - 16790\gamma = + 234.50 \ldots\ldots\ldots \text{I}$$
$$254.5\alpha + 21.49\beta - 1216\gamma = - 21.93 \ldots\ldots\ldots \text{II}$$
$$16790.0\alpha - 1216.00\beta + 72545\gamma = + 629.30 \ldots\ldots\ldots \text{III}$$

Whence we obtain:

$$\alpha = + 0.99$$
$$\beta = + 13.75$$
$$\gamma = + 0.468$$

Hence the most probable values of:

$$1/K = 8.0 + 0.99 = 8.99$$
$$A = 336 + 14 = 350$$
$$t_1 = 2 + 0.47 = 2.47$$

Hence the equation to the curve of growth for the first nine months of the extra-uterine life of South Australian females is found to be:

$$\text{Log}_{10} \frac{x}{350 - x} = 0.111\ (t - 2.47) \ldots\ldots\ldots\ldots (3)$$

Comparing this equation with that (equation 2) found for males, we observe that although the infantile growth-cycle for females is no smaller in magnitude than that for males (i.e., the total growth due to it is no less when completed) yet it is slower in development, since K, which is a measure of the velocity of the

growth-process, is only 0.111 for females, while it is 0.136 for males. Corresponding with this we find that the period at which the cycle is half completed is later (2.47 months after birth) in females than it is in males (1.66 months after birth). The fact that the period of gestation is slightly longer for females than for males is also doubtless to be attributed to the same factor.

In the following table (Table 13) the observed weights at various ages are compared with those calculated from the above formula.

TABLE 13. FEMALES

AGE OF INFANT IN MONTHS	WEIGHT IN OUNCES		Δ = DEVIATION FROM CALCULATED VALUE
	Observed	Calculated	
0	121	121	± 0
1	153	142	+11
2	168	164	+ 4
3	188	187	+ 1
4	209	209	± 0
5	224	230	− 6
6	253	249	+ 4
7	263	267	− 4
8	270	282	−12
9	300	295	+ 5
10	315	305	+10
11	335	314	+21
12	345	321	+24

The agreement between the observed and calculated values for the first nine months is very good. The "probable deviation" between observation and theory is ± 2.2 ounces.

7. The Relationship of the Post- to the Pre-Natal Curve of Growth for South Australian Infants

Having thus found an algebraical formula which adequately represents the post-natal growth of infants, as determined from direct measurements at varying periods succeeding birth, we can now proceed to exterpolate with the aid of this formula, that is to continue the observed curve a short distance backwards and ascertain whether and to what degree this exterpolated curve

agrees with the curve of pre-natal growth determined by the measurement of the weights of pre- and post-maturely born infants at birth.

The mean period of gestation for South Australian male infants is, as we have seen, 282.5 days. In equation 2, which represents the post-natal growth of males, therefore (page 27), $t = 0$ when the infant has presumably lived 282.5 days of intra-uterine life. It is true that there is much doubt whether the period of gestation measured from the onset of the last menstruation represents the true period occupied by the growth of the embryo or not,[26] but this uncertainty does not attach in nearly the same degree to the estimation of *differences* between periods of gestation with which we are solely concerned here. Taking, therefore, the value of $t = 0$ for the period of 282.5 days, and recollecting that $t = 1$ at 30 days we find that male infants born, for example, at 260 days have been delivered 22.5 days or 0.750 month prior to the period defined by $t = 0$ equation 2. In other words in order to find by exterpolation from equation 2 the "calculated" weight of an infant of this age, that is the weight which it should have if intra-uterine growth is continued uninterruptedly into extra-uterine growth, we must insert the value $t = -0.750$ and calculate from the equation the corresponding value of x. Proceeding in this way we obtain a series of "calculated" weights which if intra- and extra-uterine growth are portions of the same growth-cycle, should agree very closely with the weights actually determined by weighing infants born at the corresponding periods. A comparison of the "calculated" and "observed" weights of male infants born at varying periods of gestation follows (Table 14), the "observed" weights being taken from Table 2.

The corresponding computations for females follow (Table 15) recollecting that in this case $t = 0$ at 284.5 days. The "observed" weights are taken from Table 4.

The agreement between the observed and calculated weights is as close as could possibly be expected. There is absolutely

[26] Cf. J. W. Williams: Obstetrics, 3d ed., New York, 1912, pp. 85, 86.

no appreciable deviation of the prenatal curve of growth determined in the manner described from the continuation of the post-natal curve of growth backwards to cover the same period. This is also clearly revealed by a glance at the accompanying curves (figs. 1 and 2) in which the "calculated" curve of growth is represented by the curved line which is intersected at birth

TABLE 14. MALES

PERIOD OF GESTATION IN DAYS	t	WEIGHT IN OUNCES		Δ=DEVIATION FROM CALCULATED VALUE
		Observed	Calculated	
260	−0.75	111	110	+1
270	−0.42	117	117	±0
280	−0.08	127	126	+1
282.5	±0.00	127	127	±0
290	+0.25	137	134	+3
300	+0.58	145	142	+3
310	+0.92	146	151	−5
				$\Sigma\Delta = +3$

TABLE 15. FEMALES

PERIOD OF GESTATION IN DAYS	t	WEIGHT IN OUNCES		Δ=DEVIATION FROM CALCULATED VALUE
		Observed	Calculated	
250	−1.13	97	99	−2
260	−0.82	105	106	−1
270	−0.48	108	112	−4
280	−0.15	120	118	+2
284.5	±0.00	121	121	±0
290	+0.18	130	125	+5
300	+0.52	133	132	+1
310	+0.85	138	139	−1
				$\Sigma\Delta = +0$

by a heavy vertical line cutting the time coördinate at $t = 0$. The observed weights both for pre- and post-natal growth are indicated by small crosses (x). It is obvious that the "observed" curve exhibits no pronounced change in slope as it enters the period of intra-uterine development.

From these considerations and the curves which illustrate them it is evident: *Firstly* that the weights at birth of children

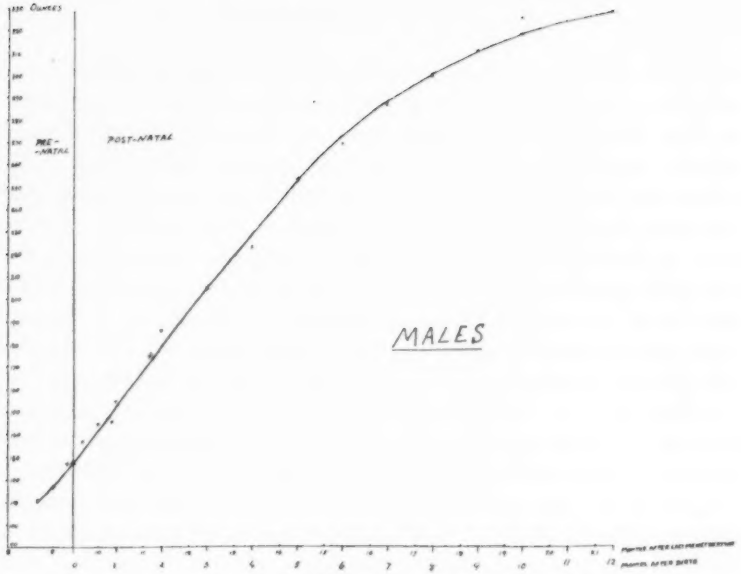

FIGURE 1

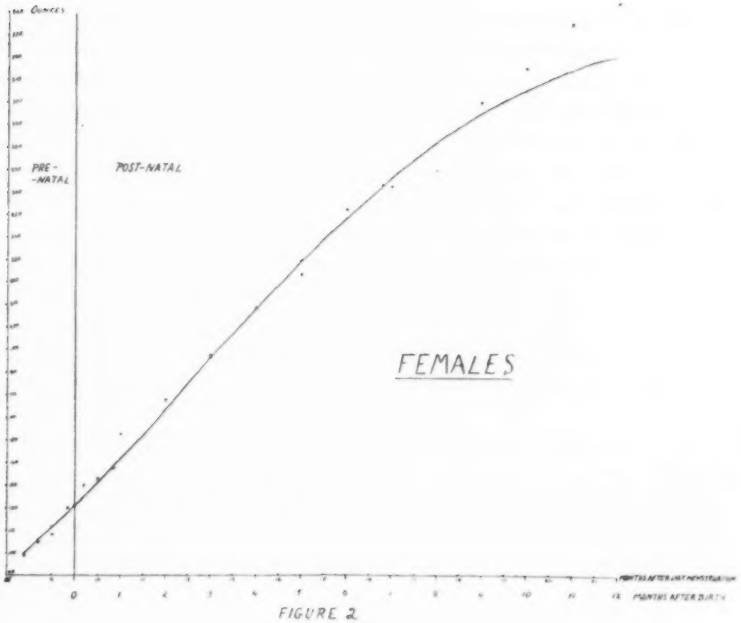

FIGURE 2

which are born *after* the normal term are identical, within very narrow limits, with the weights which they would have attained at that time had they been born at the normal period, and *secondly* that the post-natal growth-cycle as determined from weighings of infants of from 1 to 9 months of age, is continued smoothly backwards into the pre-natal curve of growth. Hence there is no indication whatever of any other growth-cycle in the pre-natal growth of man, at least in the neighborhood of birth, and, from this and from the dimensions of the cycle, it appears very probable that the cycle of growth which is determining the rate of development at birth and during the greater part of the first year of extra-uterine life is merely a continuation of a cycle which begins at or very near to the moment of actual conception, very probably at the time of implantation of the embyo.

This cycle is accompanied by the production of tissues unusually rich in phospholipines[27] and is therefore of the type which I have elsewhere designated "autokinetic."[28] Preceding this cycle, and prior to the fixation of the embryo, we may assume that there is probably a very brief cycle of chiefly nuclear growth which, as the experiments of Robertson and Wasteneys indicate[29] must be accompanied by a *decrease* of phospholipines in the tissues and is therefore of the type which I have termed "autostatic." *Following* the cycle which is interrupted by birth is another cycle which attains its maximum velocity at about 5.5 years in both sexes[30] which, as Siwertzow has shown (loc. cit.) is accompanied by a diminution of the phospholipines in the tissues and is therefore of the "autostatic" type. Following this, again, and merging into it is the final cycle, of which the maximum velocity occurs at 14.5 years in females and 16.5 years in males and which culminates with the cessation of normal growth and the attainment of adult weight. Having regard to the alternation of auto-

[27] D. I. Siwertzow: Dissertation, St. Petersburg, 1904. Cited after Biochem. Zentralbl, Bd. 2. (1904), p. 310.

[28] T. Brailsford Robertson: Arch. f. Entwicklungsmech., 37 (1913), p. 497.

[29] T. Brailsford Robertson and Hardolph Wasteneys: Arch. f. Entwicklungsmechanik, 37 (1913) p. 485.

[30] T. Brailsford Robertson: Arch. f. Entwicklungsmechanik, 25 (1908), p. 581.

kinetic and autostatic cycles which occurs during the first three cycles of growth it would appear probable, although no direct evidence exists, so far as I am aware, to this effect that this final growth-cycle is of the "autokinetic" type. Carcinomatous growth is demonstrably of the "autostatic" type[31] and it is therefore inviting to suppose that the growth of carcinoma represents an "autostatic" cycle superimposed upon the normally final "autokinetic" growth cycle of man. However this may be it is evident that there are probably four and certainly not less than three growth-cycles in the normal development of man, namely:

I. Very brief "autostatic," probably preceding implantation of the embryo.

II. Lasting from nearly the beginning of development until nearly the end of the first year of extra-uterine life. Maximum velocity at 1.66 months in males and 2.47 months in females, "autokinetic."

III. Starting during or close to the completion of the first year of extra-uterine growth and partially fusing into the succeeding cycle. Maximum rate at about 5.5 years in both sexes, "autostatic."

IV. Maximum velocity at about 14.5 years in females and 16.5 years in males. Culminating in the attainment of adult weight. Probably "autokinetic."

8. The Non-Existence of a "Critical Period" in the Normal Intra-uterine Development of Man

As I have stated in the introduction, Read (loc. cit.) has shown that there is certainly one, and there are possibly more growth-cycles which comprise the intra-uterine growth of the guinea-pig and culminate before the post-natal cycle begins. This latter cycle, in the guinea-pig is interrupted shortly after its commencement by birth. At the point of junction of these

[31] T. Brailsford Robertson and Theo. C. Burnett: Proc. Soc. Exper. Biol. and Medicine, New York and San Francisco, Dec., 1912, and April, 1913, Journ. of Exper. Medicine, 17 (1913) p. 244. T. Brailsford Robertson: Arch. f. Entwicklungsmech., 37 (1913), p. 497.

cycles there is a "critical period" distinguished by a marked tendency to premature delivery of young, possibly through a failure of the two cycles to "link up" properly.

From the preceding considerations it is evident that there is no trace of such a juncture of cycles (at any rate subsequently to implantation) in the intra-uterine growth of man, and if the "critical period" in the intra-uterine growth of guinea-pigs is really attributable to the juncture of cycles with which it coincides, then since no such juncture occurs in human intra-uterine growth we might expect to find no critical period in the intra-uterine growth (subsequent to implantation) of the human being.

A tendency for premature deliveries to occur at a certain period rather than at any other would be presumptive evidence of a "critical period" in the intra-uterine growth of man. No such phenomenon occurs, however, notwithstanding the mistaken impression of some obstetricians to the contrary.[32] This is shown by the pronounced *unimodality* of the frequency-curve[33] for the period of gestation which is displayed by the following figures (Tables 16 and 17) derived from Tables 1 and 3.

There is evidently only *one* period, the "normal" period at which the percentage of infants delivered by normal mothers attains a maximum. Subsequently to implantation of the embryo there is no evidence of a "critical period" in the intra-uterine growth of man.

[32] It may be contended that by excluding those infants which died within one week of birth I have excluded the very group of deliveries which might be expected to reveal bimodality of the frequency-curve of the period of gestation. The deliveries thus rejected were, however, relatively few in number and displayed no special tendency to occur at a period different from the "normal" period of gestation. Their rejection is rendered necessary by the fact that they represent not infrequently the fruit of pregnancies which are affected by maternal abnormality. Were there any decided tendency, however, for deliveries, within the limits comprised in the accompanying tables (16 and 17), to fall into two groups, a certain proportion of the infants delivered at the abnormal period would certainly survive, since premature delivery within these or even more extreme limits is not an insuperable obstacle to subsequent development, and maldevelopment at a "critical period" of intra-uterine growth might be expected to occur in varying degrees resulting in the delivery of many infants not sufficiently maldeveloped to render the maintenance of life impossible.

[33] Cf. C. B. Davenport loc. cit.

TABLE 16. MALES

PERIOD OF GESTATION IN DAYS	PERCENTAGE OF ALL INFANTS NOT EXCLUDED BY CHAUVENET'S CRITERION (247) BORN AT THE DESIGNATED PERIOD
250	0.8
260	8.9
270	15.4
280	32.0
	— mode
290	31.6
300	6.5
310	3.6
320	1.2
	100.00

TABLE 17. FEMALES

PERIOD OF GESTATION IN DAYS	PERCENTAGE OF ALL INFANTS NOT EXCLUDED BY CHAUVENET'S CRITERION (264) BORN AT THE DESIGNATED PERIOD
240	1.1
250	2.3
260	3.8
270	12.1
280	30.3
	— mode
290	32.6
300	11.4
310	5.3
320	1.1
	100.0

9. The Existence of a "Critical Period" in the Latter Half of the First Year of the Extra-uterine Development of Man

Subsequently to the implantation of the embryo, the guinea-pig passes through a complete growth-cycle in utero and enters upon a second before birth. Man, on the contrary, is born before his first growth-cycle, subsequent to implantation, is half completed. Corresponding to this we find that the guinea-pig is born in a relatively adult condition of development.[34] It can run about and is not dependent upon its mother for nutrition within 4 days after birth. The "critical period" which some-

[34] J. Marion Read: Univ. of Calif. Publ. Zoology, 9 (1912), p. 341.

what antedates birth in the guinea-pig, therefore, corresponds to a developmental stage which is not attained by a child until some time after birth. If the "critical period" in the intra-uterine growth of the guinea-pig originates in the difficulty with which a linkage of growth-cycles is accomplished, we should expect to find a similar "critical period" in the latter half of the first year of the extra-uterine growth of man, at which period, as a glance at figures 1 and 2 reveals, a notable "slackening off" of the growth-process occurs, preceding a fresh acceleration in the second year which represents a portion of a second extra-uterine growth-cycle.

That the latter half of the first year of extra-uterine growth is really a "critical period" in the development of man is shown by the investigations of Macgregor[35] who has determined the relationship of weight to age in over 1700 infants admitted to the City of Glasgow Fever Hospital during the years 1907–1908. Macgregor finds that for children under one year of age the weight on admission increases fairly uniformly from 3 to 6 months and is tolerably close to the average for Glasgow children of the same age. After 6 months, however, the curve of growth has its continuity suddenly broken, descends to a relatively low level and only regains its natural position as the end of the first year is reached. Evidently children who fall victims to zymotic disease during the second half of the first year of extra-uterine growth tend to be of markedly subnormal weight before any loss of weight due to the disease itself has occurred. Moreover the incidence of measles, whooping cough, and scarlet fever reaches a maximum at the eighth and ninth months while diphtheria and cerebro-spinal meningitis, although these diseases rarely occur during the first year show a maximum incidence during the sixth and seventh months of the first year. From these facts it appears *firstly* that there is a tendency for a certain proportion of infants to be of markedly subnormal weight between the seventh and the tenth months and *secondly* that these subnormally developed infants are selectively affected by certain

[35] A. S. M. Macgregor: Proceedings of the Royal Philosophical Society of Glasgow, 21st April, 1909.

zymotic diseases. On comparing Macgregor's growth-curve of infants under one year of age who have contracted zymotic disease with Read's growth-curve of prematurely delivered guinea-pigs it is impossible not to be struck by their remarkable similarity.

It might be imagined that the tendency of a proportion of infants to exhibit underweight at from seven to ten months is attributable solely to the fact that weaning "normally" (i.e., physiologically) should take place at this period, that the digestive disturbances consequent upon change of diet affect a certain proportion of children more severely than others and that these children are selectively affected by zymotic disease. These considerations, however, do not suffice by themselves to explain the phenomena observed by Macgregor, for in the first place, as he points out, bottle-fed infants supplied with milk from the city milk-depots of Glasgow show no loss of weight during the seventh to tenth months at all comparable with the subnormality exhibited by the infants admitted to the fever hospital. Therefore bottle feeding does not affect average infants more adversely during the seventh to tenth months than at any other period. Now under the conditions pertaining in a modern city the weaning of infants is by no means usually delayed until the "physiological" period. From the data collected in Birmingham by H. W. Pooler[36] it appears that not over two-thirds of the children of poor parents are breast-fed, while a still smaller proportion of the children of wealthier parents are breast-fed. Among those infants which are breast-fed weaning occurs at a very great variety of ages. Infants of subnormal weight, owing to digestive disturbances, should therefore be distributed fairly evenly among all ages during the first year unless bottle feeding tends to have a more deleterious effect upon infants between seven and ten months of age than at any other period in the first year which, as we have seen, is not the case.

It may be pointed out, also, that it is undoubtedly by no means accidental that the "physiological age" for weaning approximately coincides with the termination of one growth-cycle and

[36] H. W. Pooler: Sixth Annual Report of the Birmingham Infants' Health Society, 1913, p. 33.

the inauguration of a second. It is indeed highly probable that a change from one growth-cycle to a succeeding cycle involves profound changes in the metabolism of the organism and pronounced changes in physiological habit or mode of development might be expected to occur at periods coinciding with the deeper-seated metabolic changes. From this point of view it is noteworthy that whereas the physiological age of weaning is delayed in infants until the latter half of the first year of extra-uterine growth, a period after birth approximately coinciding in length with the period of gestation, in the guinea-pig, in which the period of gestation is 67 days, there is no definite "physiological" period of lactation, and weaning may take place within 4 days after birth without resulting in injury to the young.[37] We may infer that the need for a maternal supply of nutrition approximately coincides in duration, both in the guinea-pig and in man, with the "autokinetic" growth-cycle which succeeds the implantation of the embryo.

10. Summary

1. I have estimated the latter part of the curve of pre-natal growth and the earlier part of the curve of post-natal growth of South Australian infants from the weights of infants born somewhat prior to or later than the normal period of gestation.

2. The curve of early post-natal growth thus determined is identical with the post-natal curve of growth for South Australian infants determined by weighing the infants from birth to 9 months of age. The curve of pre-natal growth estimated in the above manner is identical with the continuation backwards of the curve of post-natal growth.

3. The mean period of gestation for 247 South Australian males is 282.5 days after the onset of the last menstruation with a "probable error" of $\pm$ 0.55 days; that of 264 South Australian females is 284.5 $\pm$ 0.57 days. The "standard deviation" of periods of gestation culminating in the delivery of males is 12.7 days, that of periods of gestation culminating in the delivery of females is 13.8 days.

[37] J. Marion Read: loc. cit.

4. The mean weight of South Australian male infants at delivery is 127.3 ounces (= 3608 grammes) with a variability of 14.3 per cent; that of South Australian female infants at delivery is 121.2 ounces (= 3435 grammes) with a variability of 14.5 per cent.

5. British infants born in South Australia are from 8 to 10 ounces heavier at birth than British infants born in the British Isles. Anglo-American infants born in the eastern United States are intermediate, in weight at birth, between British infants born in the British Isles and those born in South Australia.

6. This superiority in weight of South Australian infants is maintained in varying proportion throughout the first year of post-natal growth.

7. There is no indication whatever of more than one "growth-cycle" (sigmoid curve of growth) during the intra-uterine growth of man subsequently to implantation of the embryo. This "growth-cycle" is interrupted by birth when it is not yet half completed and culminates towards the end of the first year of post-natal life. The magnitude of this growth-cycle (that is the extent of growth due to it) is approximately equal in males and females, but it is slower in development in females than in males.

8. There are probably four and certainly not less than three growth-cycles in the normal development of man, namely:

I. Very brief, "autostatic," probably preceding implantation of the embryo.

II. Lasting from nearly the beginning of development until nearly the end of the first year of extra-uterine life. Maximum velocity at 1.66 months in males and 2.47 months in females, "autokinetic."

III. Starting during or close to the completion of the first year of extra-uterine growth and partially fusing with the succeeding cycle. Maximum rate at about 5.5 years in both sexes, "autostatic."

IV. Maximum velocity at about 12.5 years in females and 14.5 years in males, culminating in the attainment of adult weight. Probably "autokinetic."

9. There is no "critical period" in the intra-uterine development of man at which maldevelopment and premature delivery are more liable to occur, in infants born by normal mothers, than at any other.

10. There is a "critical period" in the latter half of the first year of the extra-uterine growth of man during which an exceptional proportion of infants are liable to be subnormal in weight independently of the time of weaning. These subnormal infants are selectively attacked by certain zymotic diseases. This "critical period" is probably attributable to a certain difficulty with which the two growth-cycles which meet at this period "link up" with one another.

VARIATIONS IN CORONARY PRESSURE AND THEIR BEARING ON THE RELAXATION RATE OF THE VENTRICLES

ALEXANDER L. PRINCE

From the Physiological Laboratory of the Yale Medical School

Of the numerous theories which ascribe a suction pump action to the heart during the diastolic phase, one has singularly persisted. This theory, first advocated by Ernst Brücke, is based on the assumption that the reinjection of the coronary system during diastole with blood at a high pressure causes an active dilatation of the ventricular chambers.

Earlier observations bearing directly on this topic have yielded conflicting results.[1]

Martin and Donaldson,[2] Henderson,[3] Von den Velden[4] and Lehndorff[5] have established beyond doubt the purely passive nature of diastole. In view of their investigations, the opinion that coronary tension can to any extent influence ventricular dilatation becomes untenable. Yet the fact that this view persists in modern text books, justifies the present experiments.

The following extracts will serve to illustrate the arguments upon which this theory is based. Howell[6] in a discussion of the suction action of the heart says:

> The heart in contracting exerts a force greater than that of the blood in the coronary vessels, and probably, therefore, these vessels are emptied and their cavities obliterated in part. At the beginning of diastole

[1] For a review of the literature up to 1904, the reader is referred to E. Ebstein, Ergebnisse der Physiologie, Dritter Jahrgang, II Abteilung, pp. 121, 194.

[2] Martin and Donaldson: Studies from the Biological Laboratory, Johns Hopkins University, 1887, iv, 37.

[3] Yandell Henderson: American Journal of Physiology, 1906, xvi, 325.

[4] Von den Velden: Zentralblatt für Physiologie, 1906, xx, 73.

[5] Lehndorff: Deutsches Archiv für Klinische Medizin, 1914, cvi, 75.

[6] W. H. Howell: A Text Book of Physiology, 5th Edition, 1913, p. 551.

they are reinjected with blood under a pressure of perhaps 100 mm. of mercury, and this fact seems to offer a probable explanation for a partial dilatation of the ventricular cavity and a production of negative pressure in the brief interval before the opening of the auriculo-ventricular valves.

In Hirschfelder's well known work,[7] this statement occurs:

> The walls of the heart are sufficiently rigid and sufficiently provided with elastic fibers to resume their shape like a rubber ball, and on the other hand, *the pressure in the coronary arteries tends to hold them distended as though by a wire frame.* (Italics mine.)

Although the latter view differs somewhat from the first as to the mechanics involved, the end result assumed in both instances is the same: an active dilatation of the heart dependent on coronary tension.

Howell and Ely[8] have shown, in the isolated heart of the dog, that the duration of systole and diastole is practically uninfluenced by variations in arterial pressure. In the absence of variations in diastolic time, if coronary tension is a factor in the production of an active diastole, changes in arterial pressure should cause variations in the relaxation or filling rate of the ventricles. On the basis of the "wire cage" hypothesis the rate of ventricular relaxation should bear some proportion to the coronary pressure as the elasticity of the cage would increase proportionately to the tension in the coronary vessels. Likewise, if the sudden increase in the turgidity of the heart walls which accompanies the inception of diastole is capable of aiding in the dilatation of the ventricular cavities, a relaxation rate proportional to the coronary pressure would be expected. The higher the coronary tension, the more rapidly should this erectile process take place.

In the present paper are given the results of experiments in which the behavior of the ventricles under variations of coronary pressure was studied, with special reference to their relaxation rate.

[7] A. D. Hirschfelder: Diseases of the Heart and Aorta, 1910, p. 11.

[8] Howell and Ely: Studies from the Biological Laboratory, Johns Hopkins University, 1882, ii, 453.

The method used is, with slight modifications, similar to the one described recently by Henderson and Prince.[9] The advantages of this method for this particular problem lie in the ease with which the temperature, venous pressure and intraventricular systolic resistance can be controlled. The latter never exceeds the maximal diastolic pressure. This abnormally low resistance during systole, however, cannot be considered as detrimental to the results.

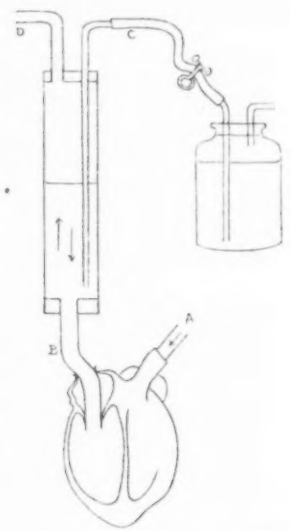

Fig. 1. A, Aortic cannula; B, Cannula inserted into ventricle; C, Syphon for the regulation of venous pressure; D, Tube to recording tambour.

The experiments were performed with the excised heart of the cat. The animals were killed by decapitation and the heart removed after ligation of the pulmonary artery. A cannula was inserted into the severed aorta and perfusion immediately begun. The perfusion fluid consisted of equal parts of defibrinated sheep's blood and Tyrode's solution, impregnated with a half volume of CO_2 and with oxygen to the point of saturation. Extreme care was taken to prevent variations in temperature, all fluids coming in contact with the heart being kept at 37°C. Arterial pressure variations were obtained by air pressure applied directly to the perfusion fluid and recorded with a mercury manometer connected close to the aortic cannula. The intra-ventricular volume changes were obtained by means of a cylindrical vessel fitted at its inferior extremity with a glass cannula of suitable length and bore (fig. 1). This cannula was inserted through a slit in the auricular appendage into the ventricle. The closure of the auriculo-ventricular valve about this tube prevented regurgitation into the auricles. The oscillations of the column of fluid in the cylinder

[9] Henderson and Prince: Heart, 1914, v, 217.

were recorded on a rapidly revolving smoked drum by means of a Marey tambour covered with loosely applied rubber dam and fitted with a very light lever. The venous pressure, as indicated by the mean height of the fluid in the cylinder was maintained at 150 mm. saline in experiments on the left ventricle and at 50 mm. on the right. These pressures, as shown by Henderson and Prince[10] are the optima for the isolated cat's heart. The following determinations were made: 1. The heart

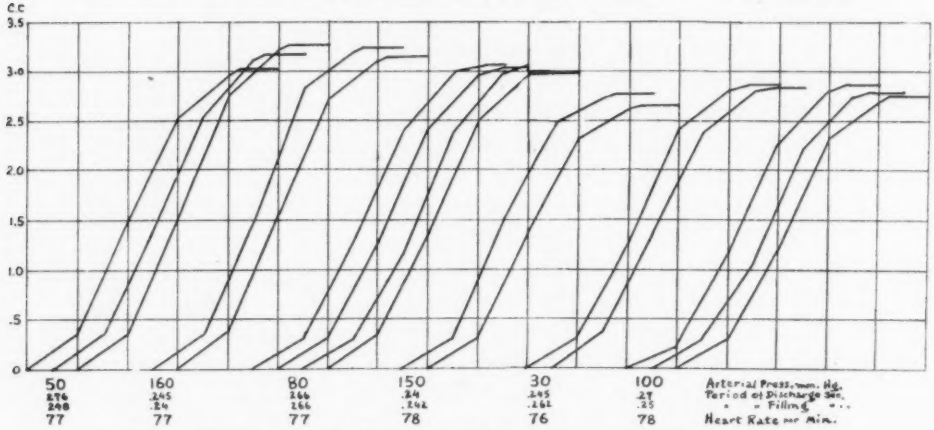

Fig. 2. Experiment I. Right ventricle. Venous pressure 50 mm. saline. Curves showing the relaxation rate of the right ventricle under variations of arterial pressure. Data obtained from intraventricular volume tracings. Under each group of curves are given the arterial pressure, the average duration of systolic discharge and diastolic filling and the heart rate. The intervals between adjacent ordinates represent 0.059 sec.

rate. 2. The duration of relaxation or filling of the ventricle (Diastole minus Diastasis). 3. The rate of relaxation of the ventricle (in cubic centimeters per equal intervals of time).

Observations were taken at intervals never more than three minutes apart, as in the excised heart the coronary flow gradually decreases in proportion to the length of the experiment. Controls on the rate of perfusion showed that this factor becomes negligible in view of the short duration of each series of observations, the total time never exceeding thirty minutes.

[10] Henderson and Prince: Heart, loc. cit.

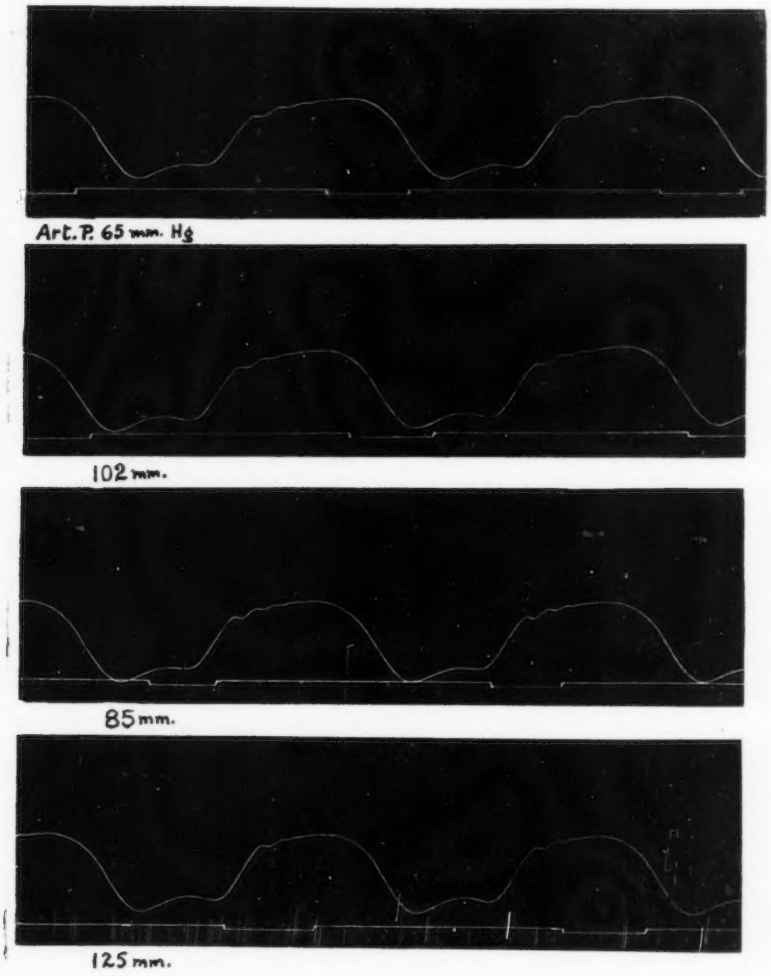

Fig. 3. Experiment II. Left ventricle. Venous pressure 150 mm. saline. Note uniformity of diastolic relaxation in the presence of marked variations in the duration of systole. Upstroke: Systole. Downstroke: Diastole.

In Experiment I (fig. 2), on the right ventricle, the arterial pressures successively applied were: 50, 160, 80, 150, 30, and 100 mm. Hg. Slight variations in the rapidity of ventricular relaxation occur, which, however, bear no relation to the degree of coronary tension. As a whole the results are negative.

In Experiment II (fig. 3), on the left ventricle, the successive pressure changes were: 65, 102, 85 and 125 mm. Hg. As in all other observations the diastolic relaxation rate, although showing moderate variations, bears no relation to the coronary pressure changes.

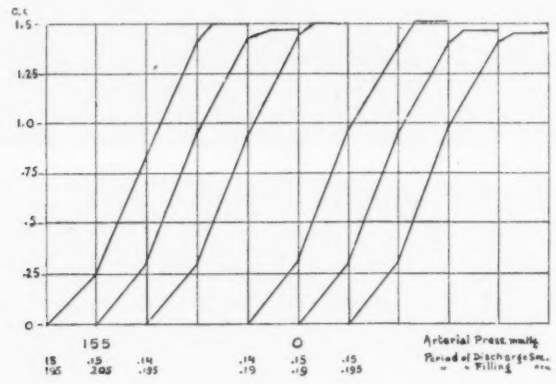

Fig. 4. Experiment III. Right ventricle. Venous pressure 50 mm. saline. Arterial pressure lowered from 155 to 0 mm. Hg. In this diagram the intervals between adjacent ordinates equal 0.059 sec.

Five other experiments on the right and left ventricles yielded similar results.

Experiment II is interesting from the standpoint of the time relations of systole and diastole. The heart exhibited a state of unusually high tonus with marked prolongation of systole. In this case the systolic time showed a distinct decrease at the higher pressures whereas the diastolic time remained practically unchanged. This observation speaks strongly in favor of a purely passive diastole, not associated with the active me-

tabolic changes formerly ascribed to this phase of the cardiac cycle by certain investigators.[11]

This experiment is in marked discrepancy with the observations of Howell and Ely[12] but is so exceptional as not, I believe, to invalidate the generality of their conclusions.

It has been shown by Knowlton and Starling[13] and others, that at excessively low arterial pressures the efficiency of the heart is markedly impaired. If, however, the heart is subjected to these low pressures only for a short period of time, this period being preceded by a phase of normal pressure, maximal efficiency can be obtained for a few beats at an arterial pressure of zero.

To determine the possible effect of extreme coronary tensions on the rate of diastolic relaxation, the arterial pressure was suddenly reduced from 155 to 0 mm. Hg. in an experiment on the right ventricle (exp. III, fig. 4) and from 140 to 0 mm. Hg. on the left. The same negative results were obtained.

CONCLUSIONS

The relaxation rate of the ventricles is not affected by variations in arterial pressure. This speaks against theories ascribing to the heart a suction action brought about either by the tension or changes of tension in the coronary vessels.

The expenses of this research were defrayed by a grant from the Committee on Scientific Research of the American Medical Association.

[11] Cited by E. Ebstein: loc. cit.

[12] Howell and Ely: loc. cit.

[13] Knowlton and Starling: Journal of Physiology, 1912, xliv, 206.

CONTRIBUTION TO THE PHYSIOLOGY OF THE STOMACH

XXI. The Secretion of Gastric Juice in Man

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The subject in this study, Mr. F. V., is now 29 years old, and weighs 69 kilos. He has been in good health since he entered the service of the University three years ago in the spring of 1912. His hunger and appetite and his food consumption are those of the average man of his age, body weight, and physical activities. Three years ago Mr. V's stomach was described by Dr. Potter as of the "orthotonic" type (9), and from continued observations on the tonus and the motor activities of his empty stomach, I feel certain that his stomach is in this condition today.

The reader will recall that Mr. V. has had a complete cicatricial stenosis of the oesophagus and gastrostomy since the age of seven (9). He masticates all his food in the normal way, places the masticated mass in a syringe, and in that way introduces it into the stomach through the large rubber tube kept permanently in the gastric fistula. The general oral sensibility and the gustatory and olfactory senses of Mr. V. show normal range and activity. In brief, Mr. V. is a normal man, except for the gastrostomy and the closed oesophagus. This fact is of importance, as it permits us to use Mr. V. as a type for the secretion and the chemistry of gastric juice in adult normal persons.

The present report deals only with the secretion of gastric juice. A later paper will include the studies on the chemistry of the hunger and the appetite secretions. Most of the present work was completed during June–October, 1912, but all the points

were checked up and extended during June–August, 1914, and during January–February, 1915. I thus have a great number of observations made at different seasons of the year, covering a period of three years. This should eliminate all variations due to special conditions.

METHODS

Most of the observations were made in connection with the noon day meal, that is, from 11 a.m. to 4 p.m. Mr. V's customary breakfast is eaten at 7 a.m., and consists of 3 to 4 biscuits (250–300 gr.), and about 200 cc. milk in about the same quantity of coffee. This meal is practically all out of the stomach in 3 to 3½ hours. At 10 or 10.30 a.m. 150 cc. of lukewarm water is put into the stomach, to insure complete emptying, and an hour later the observations are begun on the hunger or the appetite secretion. The evening meal is eaten at 6.30 or 7 p.m. In case of all observations in connection with the evening meal, the lunch (meat, potatoes, bread, milk, and fruit or pastry) was eaten not later than 12.30 p.m. and 150 cc. of lukewarm water was put into the stomach at 5.30 p.m.

The collection of the gastric juice. The permanent tube in the fistula extends far into the stomach cavity, and is provided with a number of slits so as to permit free access of the gastric juice. Slight pressure on the abdomen permits complete emptying of the stomach when Mr. V. is sitting or standing. The best results are obtained by draining the stomach at five or ten minute intervals, rather than letting the juice escape continuously through the open tube. This is particularly true of the observations on the hunger secretion which is ordinarily very scanty. This method has also the advantage of permitting Mr. V. to be busy with various tasks in the laboratory during the tests, as in that way his cerebral processes are more satisfactorily controlled. In many cases, however, the appetite secretion was measured by continuous outflow from the tube while Mr. V. was masticating his food, sitting down at the table, or standing up by an improvised lunch counter.

I. THE FLUID CONTENTS OF THE STOMACH FREE FROM FOOD

The normal stomach, empty of food, always contains some fluid and mucus. The normal stomach is therefore, strictly speaking, never empty. This fluid in the empty stomach is made up of (1) gastric juice, (2) saliva, (3) duodenal contents (pancreatic juice and bile). Pancreatic juice and bile are frequently absent, however. The total fluid content of the empty stomach as well as the chemistry of this fluid depends on several factors, such as the relative rate of gastric and salivary secretion, the tonus and contractions of the stomach, the rate of absorption in the stomach, and the rate of emptying of the stomach contents into the duodenum.

According to the more recent literature the fluid content of the empty stomach of normal persons varies within wide limits. Verhaegen found the average to be 10–25 cc., but occasionally as much as 50 cc. was obtained. Moritz gives higher figures, or 24–64 cc. Working on himself Moritz obtained an average of 43 cc. of fluid in the stomach in the morning, with an acidity of 0.11 per cent. Moritz points out that it is not always possible to completely empty the stomach of fluid by the ordinary stomach tube. Rehfus, Bergheim and Hawk have very recently reported figures on this in normal persons, the fluid in the stomach at 8 a.m. in the morning varying from 30 cc. to 180 cc. It is not clear from their data whether these figures represent one test or the average of a great number of tests on each person. If they represent only one test on each person, they are of doubtful value, as there might be considerable dilation of the stomach with influx of bile, if the person is not used to swallowing the stomach tube; and unless the persons were used to going without breakfast there would in all probability be considerable secretion of appetite gastric juice in the morning by the persons merely thinking of food. It is obvious that the continued finding of 150–180 cc. of fluid in the empty stomach of healthy adults would seriously question the generally accepted view of clinicians that in health the fluid in the empty stomach (in the morning) should not greatly exceed 20 cc.

My own results on Mr. V. are presented in Table I. There

are in all the groups a sufficient number of tests to give value to the average figures. It might be stated that most of these tests were made in connection with other lines of inquiry (hunger mechanism, action of bitters, appetite secretion, etc.), and not primarily for the purpose of determining the fluid contents of the empty stomach.

TABLE I

Fluid contents of the empty stomach of Mr. V. at different times of the year and the day

DATE	TIME OF DAY	NO. OF TESTS	CONTENTS OF EMPTY STOMACH, CC.		
			Low	High	Average
1912 June–August	Noon	45	10	35	19
1914 June–October	Noon	81	8	40	18.6
	Evening	55	9	36	16.2
1915 Jan.–February	Noon	20	8	17	12
	Morning	25	13	38	23

The data in Table I seems to show that:

1. The fluid contents of the empty stomach of Mr. V. varies considerably from time to time, but that the general average does not exceed 20 to 25 cc.

2. The gastric content is on the whole greater during the summer than during the winter months.

3. The gastric content is more abundant in the morning before breakfast than at noon before lunch.

In the case of Mr. V. the swallowed saliva is not a factor, as the oesophagus is completely closed. We are therefore dealing only with the factors of gastric tonus, continued gastric secretion, and the entrance of duodenal content. I am inclined to think that the gastric tonus is the most important item. The continuous secretion of gastric juice in the empty stomach of Mr. V. varies in rate from 2 cc. to 50 cc. per hour, yet the fluid content of the empty stomach may be as great with the low as with the high rate of secretion. Apparently, it is a question not only of rate of gastric secretion but also of the rate of emptying into the duodenum, and this passage of the gastric contents into the intestines depends directly on the gastric tonus. In all probability it is this factor (gastric tonus) which is mainly responsible

for the greater abundance of the gastric content in the morning than at noon or evening, and during the summer in comparison with the winter months. So far as I know, however, we have no direct proof that the tonus of the empty stomach is less in the early morning than later in the day, and less during the warm summer than during the cold winter months. But since vigorous activity leads indirectly to increased tonus of the empty stomach through some change in the blood (10), the above surmise is more than a guess. It is also, I think, a fairly uniform experience that after a night of restful sleep the hunger sensation, which depends directly on gastric tonus (11) is feebler than later in the day. It is the author's experience that, partaking of dinner at 6 p.m. the hunger sensation is stronger at 11–12 o'clock at night before going to sleep than at 5–7 in the morning after a night's rest, despite the fact that in the morning the stomach has been free from food for a longer time.

The contents of the empty stomach of Mr. V. always contains some free HCl and pepsin. But the acidity is low, never exceeding 0.2 per cent, and frequently as low as 0.05 per cent. In the morning the gastric content is frequently, during the day rarely, mixed with bile. This also points to a greater tonus relaxation of the stomach in the morning.

II. THE CONTINUOUS SECRETION OF THE EMPTY STOMACH

Continued secretion of gastric juice in the absence of food in the alimentary tract, and in the absence of cerebral processes relating to appetite ("psychic" stimulation), is a well known phenomenon in certain types of gastric disorders, but it is generally assumed by physiologists that in the absence of psychic stimulation, the gastric glands cease to secrete almost as soon as the stomach is emptied of chyme, and that the glands remain practically quiescent up to the next feeding. The quiescence is supposed to be sufficiently complete to render the surface of the stomach alkaline, due to the continued secretion of alkaline mucus. To the extent that this view is anything more than an assumption, it is based essentially on the studies of Pawlow and his pupils on dogs. Pawlow frequently emphasizes the

fact that not a drop of gastric juice flows from the stomach unless there is food or other stimuli in the stomach or unless the appetite mechanism is called into play.

Later Boldyreff (4) reported that on continued starvation the gastric glands exhibit periodic activity, and if the starvation is maintained for more than three or four days the secretion of the gastric gland becomes continuous. In gastric fistula cases of normal persons no specific study has been made of the continuous secretory activity of the empty stomach, so far as I can learn from the literature, but in some instances (Kaznelson, Hornborg) there are indications of a slow continued secretion even when the stomach had been free from food for hours. In the first report (9) of the studies on Mr. V. in 1912 it was noted that "during the hunger contractions of the empty stomach the secretion of mucin is increased, and there is a decrease of hydrochloric acid, but the secretion is rich in pepsin. In no instance was the stomach found free from gastric juice, that is a fluid containing pepsin, free hydrochloric acid and mucin in varying concentrations. There are periods of spontaneous secretion of gastric juice in the empty stomach, the acidity of which is nearly equal to that of the psychic secretion." During the five days complete starvation experiment on Mr. L. and the author both of us noted that our stomachs contained some acid gastric juice night and day throughout the entire period, but as this observation was incidental we did not determine the rate and quantity of this continuous secretion (12).

Last year Rehfus, Bergheim and Hawk, working on apparently normal persons and using the Ewald meal and the Rehfus stomach tube, reported many cases in which the secretion of gastric juice continued for one-half to one hour or more after all the food had left the stomach. Unfortunately they give no data on the rate or quantity of this secretion, or the methods by which the appetite or psychic factor was controlled. It is not even clear from their report whether or not the stomach was completely emptied of this juice at each test. The acidity figures reported show that the percentage of hydrochloric acid of the spontaneous secretion was practically the same as that of the test breakfast chyme. The acidity is much too low for

pure human gastric juice. Their gastric content was therefore mixed with saliva or pancreatic juice, or else the rate of the gastric secretion did not exceed 10–12 cc. per hour.

Most of my tests on Mr. V. were made between 10 am. and 4 p.m., the usual breakfast of coffee, milk and biscuits being taken at 7 a.m. A few tests were made 9–12 a.m., in which case Mr. V. did not take any breakfast. The following typical results may be cited as illustrations:

Experiment 25, showing maximum rate of secretion of empty stomach. Breakfast 7 a.m.; 100 cc. water into stomach at 10 a.m.

11.00 a.m.	12 cc. in stomach, clear
11.10	8 cc. in stomach, clear
11.20	7 cc. in stomach, clear
11.30	8 cc. in stomach, clear
11.40	7 cc. in stomach, clear
11.50	8 cc. in stomach, clear
12.00 m.	6 cc. in stomach, clear

Starting to masticate a palatable lunch.

12.10 p.m. = 38 cc. gastric juice + trace of bile.

Experiment 17, showing an average rate of secretion of empty stomach. No breakfast; water into stomach at 7 a.m. and 10 a.m.

11.00 a.m.	10.0 cc. in stomach, clear
11.10	2.0 cc. in stomach, clear
11.20	1.0 cc. in stomach, clear
11.30	0.5 cc. in stomach, clear
11.40	0.3 cc. in stomach, clear
11.50	0.5 cc. in stomach, clear
12.00 m.	1.0 cc. in stomach, clear
12.10 p.m.	1.0 cc. in stomach, clear
12.20	0.5 cc. in stomach, clear
12.30	0.3 cc. in stomach, clear
12.40	0.3 cc. in stomach, clear
12.50	0.4 cc. in stomach, clear
1.00	0.5 cc. in stomach, clear
1.10	1.0 cc. in stomach, clear
1.20	0.5 cc. in stomach, clear

Starting to eat lunch.

1.30 = 22 cc. gastric juice, clear.

Experiment 45, showing minimum rate of secretion of empty stomach. Breakfast 7 a.m.; water into stomach at 10 a.m.

10.30 a.m.	12.0 cc. fluid in stomach
11.00	1.5 cc. gastric juice
11.30	1.5 cc. gastric juice
12.00 m.	1.0 cc. gastric juice
12.30 p.m.	1.5 cc. gastric juice

Starting to masticate the lunch.

12.40 = 46 cc. gastric juice

Experiment 4, showing spontaneous fluctuations in the rate of secretion of the empty stomach. Breakfast 7 a.m.; water into stomach 10 a.m.

12.00 m.	16 cc. fluid in stomach
12.30 p.m.	3 cc. gastric juice
1.00	4 cc. gastric juice
1.30	3 cc. gastric juice
2.00	8 cc. gastric juice
2.30	10 cc. gastric juice
3.00	7 cc. gastric juice
3.30	4 cc. gastric juice
4.00	1 cc. gastric juice

Starting to masticate lunch.

4.10 = 35 cc. gastric juice.

In general more gastric juice is obtained from the empty stomach, if the stomach is emptied every 5 or 10 minutes, than if it is emptied every 30 or 60 minutes. It is therefore likely that some of this secretion passes into the intestines or is actually reabsorbed in the stomach itself. It does not seem probable that the presence of a certain amount of this juice in the stomach would tend to inhibit further secretion.

The chemistry of this continued secretion will be reported on in a later paper in connection with that of the appetite gastric juice. If the secretion rate is low the free acidity is usually not over 0.20–0.25 per cent, but the pepsin concentration is nearly as great as that of the appetite gastric juice. If the secretio rate is 2–4 cc. in 10 minutes, the acidity is greater and the pepsin concentration may even exceed that of the appetite secretion. When the secretion rate is low the juice is very thick and opales-

cent, owing to the great amount of ropy mucin. The viscosity is so great that it is difficult to handle small quantities of this juice in test tubes or pipettes.

What constitutes the stimulus to the continuous gastric secretion?

1. I think it can be shown that it is not an appetite secretion. To be sure, in the case of normal and vigorous persons periods of hunger contractions and appetite sensation are present almost as soon as the stomach is emptied of food. And it is obviously difficult to so control the cerebral processes of a person that the thoughts are not diverted to food and eating, especially if it is passed the usual meal time and one's attention is at times on the stomach. This is especially true if the gastric juice is collected every 10 minutes. If the stomach is emptied every 30 or 60 minutes and the person kept very busy with matters not pertaining to food and eating I think this factor is entirely eliminated. This was done every day for two weeks at a stretch, so as to make it a mere incident or routine in the day's work. Nevertheless, the continued secretion persisted with the usual fluctuations in character and quantity. I therefore feel that the conscious appetite or psychic factor is eliminated in most of these experiments.

2. Is the secretion due to a sub-conscious vagus tonus? The vagi carry secretory fibers to the gastric glands. But we know next to nothing about the reflex or tonus control of this neuro-secretory mechanism. We know that the vagi send tonus impulses to the gastric motor mechanism (8, 13). But it does not follow that this is also the situation in regard to the gastric glands. The mechanism governing the vagus tonus has interested the writer for some time. The possible secretory vagus tonus must be subjected to direct experiments.

3. The presence of food in the intestine may be partly responsible for this continued secretion, by reflex action from the intestinal mucosa (Pawlow), or by absorptions of gastric secretions into the blood. In a 59 year old man with gastric fistula Umber obtained some secretion of gastric juice on rectal feeding with milk, sugar and eggs. Umber explains the secretion as a reflex ef-

fect from the mucosa of the large intestine. I am not convinced that purely psychic factors are excluded in his experiments. If a person is hungry it is likely he will be lead to think of food and eating by the mere act of rectal feeding. Moreover, Umber's experiments were not munerous enough to really establish the point.

4. Gastric juice itself contains mucins and proteins that are digested by the pepsin-hydrochloric of the gastric juice. It is highly probable that the acid products of this digestion yield gastric secretagogues, just as in the case of some of the digestion products of the food proteins. According to Bickel (2) amino acids given by mouth cause secretion of gastric juice. The recent work of Folin and Lyman appears to show definitely that nitrogenous digestion products are absorbed in the stomach itself. Absorbed slowly in the stomach or passed into the intestines to be absorbed there, the products of the autodigestion of the gastric juice probably furnishes chemical stimuli for a slow, but continuous gastric secretion. Which one of the above factors is of prime importance in the continuous secretion of gastric juice by the empty stomach must be determined by other lines of work.

III. THE APPETITE SECRETION OF GASTRIC JUICE

1. *The mere act of chewing indifferent substances, and the stimulation of nerve endings in the mouth by substances other than those directly related to food cause no secretion of gastric juice.*

On the above points my results on Mr. V. are in complete accord with those of Pawlow and his school on dogs, and contrary to those of a number of observers on man. The results on Mr. V. may be illustrated by the following typical experiments, presented in detail in Table II.

Richet reports secretion of gastric juice from acid stimulation in the mouth in a woman with gastric fistula and oesophageal stenosis. He also states that the introduction of food or sapid substances into the stomach via the fistula caused salivation. This must have been a purely psychic effect, unless the procedure

caused nausea. The subject was evidently a hypersensitive woman. I have never observed any of these effects on Mr. V.

In 1896 Schüle introduced the method of obtaining pure appetite gastric juice in man by emptying the stomach by means of a stomach tube, then chewing food for 15 minutes, and again emptying the stomach with the tube. He claims that the mere act of chewing and the tasting of such sapid substances as oil of peppermint, slices of lemon, and mustard cause secretion of gastric juice even in the absence of appetite. It may be remarked, however, that in the absence of depressor factors normal persons

TABLE II

Gastric juice in cc.

	TIME IN MIN.	EXP. 19	EXP. 7	EXP. 11	EXP. 27
Nothing in mouth	10	5	1.0	0.4	1.0
	10	7	0.8	0.4	0.8
	10	6	0.5	0.5	1.0
Chewing paraffin	10	5	0.4	0.2	0.9
Nothing in mouth	10	4	0.4	0.3	1.0
Vinegar in mouth	10	6	0.4	0.2	1.0
Nothing in mouth	10	5	0.5	0.3	1.0
Mustard in mouth	10	6	0.5	0.4	0.8
Nothing in mouth	10	4	0.4	0.2	0.8
Quinine in mouth	10	3	0.3	0.5	0.9
Nothing in mouth	10	5	0.3	0.3	1.0
Chewing food	10	50	24.0	17.0	44.0

invariably experience some hunger and appetite as soon as and as long as the stomach is empty of food. Troller, using Schüle's method, also reports that slices, of lemon, mustard, etc., in the mouth, as well as the mere act of chewing, cause secretion of gastric juice. In the majority of his experiments the secretion thus obtained is very slight (only about one-quarter that obtained on chewing bread), and in some of the experiments recorded in detail the acidity of the juice is so low that it must have been mixed with swallowed saliva. It is probably very difficult for the average person to avoid swallowing some saliva with mustard or acidic acid in the mouth for 10–15 minutes. And so far as I can make out from the report, Troller did not adequately control

the rate of secretion in the empty stomach when the persons had nothing in particular in the mouth. Riegel cites the case of a professional cook, in whom chewing of food (beef steak) or slices of lemon caused no secretion of gastric juice. This man showed chronic digestive disorders, however. But Riegel suggests that the absence of appetite secretion was due to a kind of permanent fatigue of the taste-secretory mechanism in consequence of his work as cook. Hornborg, working on a five year old boy with gastric fistula and nearly complete cicatricial stenosis of the oesophagus, concluded that chewing indifferent, bad tasting or strong tasting (lemon) substances did not induce secretion of gastric juice. Umber obtained no gastric secretion by chewing indifferent substances (a piece of rubber), but in one experiment alcohol in the mouth gave a slight secretion (3 cc.). It must be noted that Umber's subject was a man 59 years old, who might have been in the habit of taking alcoholic beverages with his meals.

Kaznelson, and Bickel, working on a 23-year-old girl with gastric fistula and complete cicatricial oesophageal stenosis, report that all sapid substances (quinine, asafœtida, etc.) in the mouth, even those that give rise to disgust, initiate or augment the gastric secretion. Kaznelson cites one experiment with quinine (control experiment with water) from which she concludes that bitter substances in the mouth augment the secretion of gastric juice; but her actual figures (Tables III, *a* and *b*, p. 37, 38) show, if anything, the reverse. The total secretion of gastric juice for 80 minutes with the water control (sham drinking) was 43.7 cc., while the quinine experiment yielded only 37.6 cc. for the corresponding time.

How are the above contradictory findings to be accounted for? In view of the consistently negative results of Pawlow and his students on dogs, and of Hornborg, and the writer on man, it is my belief that the investigators who report that mechanical chewing and stimulation of the nerve endings of general sensation in the mouth cause secretion of gastric juice have not eliminated the factors of appetite, swallowed saliva, and variations in the rate of the continuous secretion of the empty stomach. In man

the appetite factor is not easily controlled, except by a long series of tests in which the experimental procedure becomes a mere routine to the subject. There appears to be no direct, or unconditional reflex pathway from the mouth to the gastric gland. Unless the stimuli in the mouth initiate or augment the central processes that constitute the sensation of appetite there is no innervation of the secretory nerve fibres to the stomach. It must also be remembered that lemon juice, acidic acid, and mustard are ingredients of many food preparations, and hence may stimulate appetite secretion.

2. *The relatively slight and inconstant secretion of gastric juice produced by seeing, smelling or thinking of food.*

Bringing a tray of palatable food into the room in sight of Mr. V. has never yet caused secretion of gastric juice, no matter what the degree of hunger and appetite. It is probable that under these conditions the primary and normal effects of seeing and smelling the food are inhibited by the consciousness of the experiment, or possibly his main interest was not the food but the expiration of the experiment so that he might partake of the food. To more closely approximate normal conditions, Mr. V. was sent out to the nearby cafeteria to select the lunch that he knew he would eat shortly after returning with it to the laboratory, the rate of his gastric secretion being measured for 10 minute periods before going for the food, during the selection of, and after returning to the laboratory with it. A few typical tests secured in this way are given in Table III.

In the majority of these tests the act of selecting the ingredients for the noon day meal caused a slight and temporary augmentation of the secretion rate of the empty stomach. On the whole this augmentation was greater the greater the rate of the continuous secretion. But on some days the augmentation was absent, although Mr. V. was to all appearances in normal condition, felt hunger, and the cafeteria displayed the usual variety of food stuffs.

Pawlow reports that there are great individual variation in dogs in the amount of gastric secretion induced by seeing and smelling food. This is in all likelihood true of man, and I sus-

pect that Mr. V. belongs to the group of individuals in whom the taste of the food is the all important factor in the psychic secretion of gastric juice. I have not been able to appreciably augment the continuous secretion in Mr. V. by inducing the thought of food, for example, during a test while he is busy with other work, arresting his attention, casually, by discussing with him the taste and ingredients of his favorite dishes.

Schüle states that seeing or smelling food causes no secretion of gastric juice in normal persons. This is directly contradicted by Bulawinzew, according to the review of his paper in the *Biochemische Centralblatt* (the original paper is not accessible

TABLE III

Secretion of gastric juice on seeing, smelling, and thinking of food when hungry

	TIME IN MIN.	GASTRIC JUICE IN CC.					
		Exp. 3	Exp. 8	Exp. 12	Exp. 15	Exp. 30	Exp. 45
Selecting the lunch at the cafeteria.	10	5	0.5	0.3	0.4	0.6	0.4
	10	7	0.3	0.4	0.5	0.5	0.3
	10	6	0.5	0.3	0.4	0.4	0.4
	10	14	1.0	1.0	3.5	0.5	1.0
	10	10	1.0	0.6	2.0	0.4	1.0
	10	5	0.5	0.5		0.3	1.0
	10	6	0.3	0.4		0.4	0.7

to me). This investigator emptied the stomach by means of the stomach tube, let the subject see or smell food, and again emptied the stomach. The gastric juice thus obtained had such low acidity (0.2 per cent HCl) that it must either have been the continuous gastric secretion or the appetite gastric juice mixed with saliva. There is nothing in the review to indicate that he controlled the continuous gastric secretion. Hornborg obtained no secretion of gastric juice from the 5-year-old boy on seeing or smelling food, probably because the child always became angry when not permitted at once to eat the food shown him. Cade and Latarjet report secretion of gastric juice induced by talking to the subject about her favorite food. This subject (a young woman) is exceptional in that she virtually had an accessory

stomach, but the mucosa of the isolated stomach portion was directly exposed so that the collection of the secretions was rather difficult. Kaznelson, and Bickel, working with a 23-year-old girl with gastric fistula and stenosis of the oesophagus, reached the remarkable conclusion that anything which stimulated the olfactory sense induced secretion of gastric juice in the resting stomach. Thus they claim that smelling ammonia, acidic acid, and aromatic oils cause secretion of gastric juice. This I am absolutely unable to confirm on Mr. V. It is possible that in this young woman every gustatory and olfactory stimulus when manipulated by the investigators led to thoughts of food through idea associations.

3. *The gastric secretion induced by tasting and chewing palatable food*

(1) *The secretion rate.* I have now records of 156 tests of the appetite secretion during the 20 minutes mastication of the noon day meal. The particular ingredients of this meal were of his own selection, and varied from day to day. It usually included soup and some kind of meat and gravy, and always milk, and a dessert. These data may be presented in the following summary:

Secretion of gastric juice during 20 minutes mastication of palatable food.

Lowest	= 30 cc.
Highest	= 156 cc.
Average	= 70 cc.
Number of experiments	= 156

This gives an average rate of secretion of 3.5 cc. of gastric juice per minute. The maximum rate of secretion obtained at any time was 54 cc. in 5 minutes, or 10.8 cc. per minute; the lowest was 7 cc. in 5 minutes, or 1.4 cc. per minute. The secretion rate is proportional to the palatability of the food. Thus the secretion rate is nearly always highest in the last 5-minute period, when Mr. V. masticates the dessert, and on the day when the highest rate of secretion was noted (156 cc. in 20 minutes) Mr. V. stated that the lunch was "unusually fine."

A few typical experiments are given in detail in Table IV.

Is the above rate and quantity of appetite secretion of gastric juice typical for normal adults? So far as I can make out Mr. V. is in normal health, except for infrequent periods of headache and nervousness, the etiology of which is obscure.

TABLE IV

Rate of appetite secretion of gastric juice of Mr. V. Detail of typical experiments

EXPERIMENT NO.	RATE OF SECRETION OF GASTRIC JUICE IN CONSECUTIVE 5 MIN. PERIODS. CC.									
	Before starting chewing			During chewing				On cessation of chewing		
20	1	0.5	0.8	10	15	14	20	5	3	1.0
31				11	18	17	23	10	6	2.0
35	0.5	0.6	0.7	15	16	15	18	8	4	1.5
55	3.0	2.0	3.0	20	22	21	30	15	6	6.0
86	0.2	0.2	0.3	5	20	18	20	9	3	1.0
94	0.2	0.3	0.2	6	11	15	12	3	2	0.5
120	0.2	0.2	0.1	6	28	20	29	8	6	2.0
150	0.2	0.3	0.2	22	54	35	45	20	15	8.0

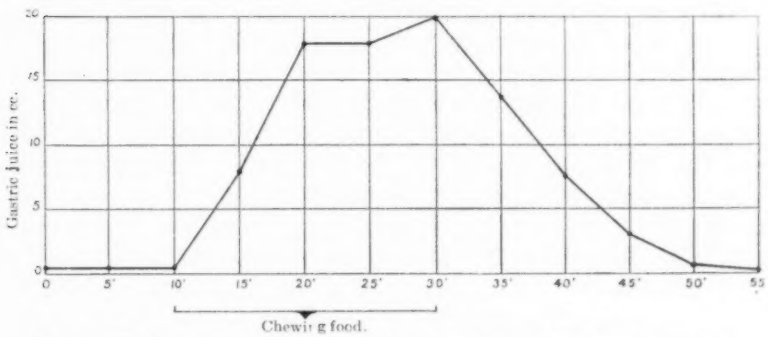

Fig. 1. Typical curve of secretion of gastric juice of Mr. V. on mastication of palatable food for twenty minutes. The gastric juice was collected at five minute intervals. The rise in the secretion rate during the last five minutes of mastication is due to chewing the dessert (fruit).

Troller reports five experiments on a person with nervous dyspepsia. Chewing beefsteak for 15 minutes yielded 55 cc. of gastric juice. Three experiments on a person with hyperacidity gave 50 cc. gastric juice in 15 minutes. This is a secretion of rate of about 3.5 cc. per minute. Chewing bread for 15 minutes yielded much less gastric juice. In the case of per-

sons with hypochlorhydria, the average secretion for 15 minutes (chewing beefsteak) was only 28 cc. In Umber's fistula case (man 59 years old) two tests with chewing beefsteak for 15 minutes yielded 73 cc. and 48.5 cc. gastric juice in 60 minutes. This low rate of secretion (about 1 cc. per minute) must be due to the advanced age and to the malignant tumor of the oesophagus. The 10-year-old girl studied by Summerfeld secreted 110–150 cc. gastric juice in 90 minutes on chewing meat or mixed food for 30–40 minutes, a secretion rate of 2–2.5 cc. per minute. The maximum secretion rate in the 23-year-old girl studied by Kaznelson and Bickel, was 5 cc. per minute, the average secretion rate being much lower. Hornborg's 5-year-old boy secreted 15–25 cc. in 30 minutes on chewing meat or apple pie. Chewing bread or milk yielded less than half this amount. The 3-year-old child of Bogen on chewing meat for 15 minutes yielded 6–22.5 cc. gastric juice, or an average rate of less than 1 cc. per minute.

These data reported by previous investigators cannot be directly compared with my results on Mr. V. for the reason that the collection of the gastric juice was not always confined to the actual period of mastication of the food. The reader will observe on examination of Table IV that the rate of the appetite secretion starts to fall almost as soon as Mr. V. ceases to masticate the food and in 15 minutes the gastric glands are in most cases down to the level of the continuous secretion. The secretion rate is highest during the actual tasting of the food.

In this respect there is a marked difference between man and dog. In the dog after 12–24 hours starvation sham feeding with meat for 5 minutes may initiate and keep up secretion of gastric juice for 3–6 hours (Pawlow, Rosemann). It is obvious that in these tests on dogs the starvation period was much longer and the hunger and appetite more intense than in the present experiments on Mr. V. Another factor is probably the greater voluntary control over attention and other cerebral processes in man.

It may be of interest in this connection to note the rates of gastric secretion that have been obtained by sham feeding in dogs. Konowaloff reports 4 cc. per minute; Schoumow-Siman-

owsky found a maximum of 5 cc. per minute; and Rosemann (in a 24 kilo dog) gives as the average 3.4 cc. per minute. Since the quantity of gastric glands even in very large dogs is probably only a third of that in the adult man, the above data seem to indicate that the gastric glands in dogs work with greater speed than the gastric glands of man.

The acidity and pepsin concentration of the gastric juice of Mr. V. are very constant. There has been practically no variations noted during the three years of observation. These will be reported on in a later paper.

(2) *The direct relation between the rate of appetite gastric secretion and the palatableness of the food.*

The mastication of bread and butter, or the taking of milk in the mouth yielded much less gastric juice than the chewing of meat. This is in line with results of previous observers on man. The taste nerve endings are evidently stimulated more intensely by the readily diffusible rapid substances in the meat. In general the desserts (pies, pudding, fruits) yielded even a greater secretion than meat. This was particularly noticeable in the case of chewing oranges. Mr. V. states that he is especially fond of oranges. The sapid substances in the orange juice probably diffuse readily and thus reach all the taste nerve endings in marked concentration.

There is no question but that the mastication of a palatable dessert at the end of a meal thus serves to augment and prolong the appetite secretion of gastric juice.

(3) *The latent period of the gastric appetite secretion.*

Pawlow and his co-workers found that the appetite gastric secretion in dogs exhibited uniformly a latent period of 5–6 minutes. The literature contains the following observations on the latent period in man.

Hornborg	3 minutes (meat)
Umber	3 minutes (meat)
Sick	6–10 minutes
Kaznelson	4–5 minutes
Bogen	4–5 minutes (meat) 9 minutes (milk)

The work on Mr. V. has brought out the following facts:

1. The latent period of the appetite secretion depends primarily on the condition of the gastric glands. *Thus if there is a continuous gastric secretion of 2–6 cc. per 10 minutes at the time mastication of the food begins, the appetite secretion shows practically no latent period at all.* The quantity of gastric juice secreted during the first 5 minutes of chewing is just as great as that secreted during the second or third 5 minute periods. On the other hand, if the continuous secretion is very low (0.2–0.3 cc. or less per 10 minutes), the appetite secretion shows a latent period of 2–4 minutes. It is therefore evident that with the gastric secretion already in progress the appetite secretion reflex exhibits no greater latent time than the neuro-muscular reflexes in general.

2. The latent period varies indirectly with the intensity of the appetite stimulation. This fact is illustrated in Experiment 150, Table IV. In that case the continuous secretion was near the lowest mark, yet the first 5 minutes of chewing yields 22 cc. gastric juice, or more than the *average full secretion rate.* But even here a latent period of 2–2½ minutes is in evidence from the fact that the second 5 minutes period yielded 54 cc. gastric juice.

IV. THE TOTAL SECRETION OF GASTRIC JUICE IN MAN ON AN AVERAGE MEAL

As stated above Mr. V. yields appetite gastric juice at minimum secretion rate, 84 cc. per hour, maximum secretion rate, 648 cc. per hour, average secretion rate, 210 cc. per hour.

Does this furnish us a clue to the total gastric secretion on an average meal in man? This question cannot be answered by direct measurements, even in cases of duodenal fistula and collection of all the chyme issuing through the pyloric opening, as the alimentary tract of such persons is far from normal, and we still have the variable factors of swallowed saliva, and of direct absorption in the stomach. In the case of dogs sham feeding alone may yield 600–700 cc. of gastric juice in 4–6

hours. But this situation is abnormal because the sham feeding does not satisfy the appetite, even though the secretion inhibits the hunger. It is therefore certain that the appetite secretion is much less when the food is permitted to reach the stomach. But when the food is allowed to reach the stomach how can we measure the total gastric secretion? Using large dogs with fistula of the duodenum, Moritz reports that the ingestion of 200 gr. of meat caused secretion of 320 cc. gastric juice in 7 hours. Part of this was undoubtedly swallowed saliva, and possibly some admixture of bile and pancreatic juice. With the same method Tobler obtained 200–300 cc. of gastric juice from feeding 100 gr. meat, part of which was undoubtedly swallowed saliva.

It seems to me that we can arrive at a very close estimate of the total average secretion of gastric juice in man on the following basis. Pawlow and his pupils have shown on dogs that the secretion curves of the main and the accessory stomach pouch run parallel. They have also shown that on a meal of meat or a mixed meal, the secretion usually reaches the maximum at the end of the first or during the second hour. Lönquist notes particularly that the secretion does not reach its maximum until toward the end of the second hour after feeding. This can mean only one thing, viz., that the rate of the hormone gastric secretion may be equal to or even exceed the rate of the appetite secretion.

On the whole, the quantity of gastric juice yielded by a dog's accessory stomach the first two hours on a moderate meal of meat, bread or a mixture of meat and bread, is about half of that secreted during the entire digestion period. This is evident from experiments reported in detail by Pawlow and his students, as well as from studies on dogs in our laboratory. This is not true if a very large quantity of food is given, or if the food contains a considerable amount of fat, as in both cases the secretion period is greatly prolonged.

I think we can safely assume that the general relations and the relative importance of the appetite and the hormane gastric juice are the same in man and dog. Pflaunder supports the view that the maximum rate of secretion in man is reached at the

end of the first or the beginning of the second hour of digestion. Sick finds that the maximum acidity of the gastric content is reached at the end of the first hour of digestion. The same is shown by the more recent studies of Rehfus, Bergheim and Hawk using the Ewald test meal on normal persons. It is obvious, however, that the acidity curve of the gastric content after a meal does not give us a direct information on the question of gastric secretion rate, because of the variable factors of swallowed saliva, fixation of the HCl by the proteins of the food, rate of entrance of the chyme into the duodenum, and the entrance of duodenal contents into the stomach (Boldyreff). Nevertheless, so far as they go, these data on normal men are on the whole in agreement with the direct measurement on normal dogs with accessory stomachs.

The total secretion of gastric juice in normal adult man on ingestion of the average dinner of meat, bread, vegetables, coffee or milk and dessert will on the above assumption be as follows:

First hour	200 cc. gastric juice
Second hour	150 cc. gastric juice
Third to fifth hour	350 cc. gastric juice
Total	700 cc. gastric juice

It should be noted in this connection that Mr. V's noon day meal is in reality the big meal or dinner. I have evidence that he secretes less gastric juice on his evening meal, probably not more that 400–500 cc., (14) and from the fact that he makes his breakfast solely on biscuits, coffee and milk, it is likely that his secretion of gastric juice on the morning meal does not exceed 250–300 cc. This would make a total of 1350–1500 cc. gastric juice secreted in 24 hours. These figures do not include the continuous secretion in the absence of food. It is of interest to note that Pflaunder arrived at practically the same figures (1500 cc., or 25 cc. per kilo body weight, in 24 hours.), basing his estimate on calculations from the acidity and volume of the gastric content at varying periods after the meal.

It need not be pointed out that the above figures are sub-

ject to great variations, depending on the food, the appetite secretion being determined primarily by the quality or taste of the food, while the hormone secretion is determined by the quantity and the chemistry of the food.

SUMMARY

1. The fluid contents of the "empty" stomach varies from 8 cc. to 50 cc. with an average of 20 cc. The quantity is greater in the morning than at noon or at 6 p.m. It is on the whole greater in the summer than in the winter months. The most important factor in these daily and seasonal variations is probably the tonicity of the empty stomach.

2. The gastric glands in the normal person are never completely quiescent. The continuous secretion varies from 2 to 50 cc. per hour. The higher figures are exceptional, but may obtain for several days in succession, again to revert to the lower figures. The vagus secretory tonus is a possible, and the autodigestion of the gastric juice itself is a probable factor in this continuous gastric secretion. The secretion itself is rich in pepsin, but when the secretion rate is very low it is poor in hydrochloric acid.

3. Chewing of indifferent substances, and stimulation of the nerve endings in the mouth by substances not related to food do not cause secretion of gastric juice, that is, these processes do not augment the continuous gastric secretion.

4. Seeing, smelling, and possibly thinking of palatable food usually cause a slight, but very transitory secretion of gastric juice.

5. The rate of secretion of gastric juice on mastication of palatable food is directly proportional to the palatability of the food. During mastication the average rate is 3.5 cc. per minute (minimum rate: 1.4 cc.; maximum rate: 10.8 cc.). On cessation of chewing the secretion rate diminishes rapidly so that in 15–20 minutes the gastric glands reach the level of the continuous gastric secretion. The chemistry of this appetite gastric juice has been practically constant during the three years of observation.

6. The latent period of the appetite secretion varies indirectly with the rate of the continuous secretion, so that when the continuous secretion is abundant the appetite secretion shows no latent period at all, while with the lowest rate of the continuous secretion, the latent period varies from 2–4 minutes. This latent period is therefore one of the processes of secretion in the gland cells, and not in the nervous mechanism.

7. On the basis of these experiments on Mr. V. on the reports of other gastric fistula cases in man and on the work of Pawlow on dogs it is estimated that an adult normal person secretes on an average meal (dinner) 700 cc. gastric juice, or an average total of 1500 cc. gastric juice in 24 hours.

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STUDIES ON THE GROWTH OF MAN

2. The Post-Natal Loss of Weight in Infants and the Compensatory Over-Growth which Succeeds It

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1. INTRODUCTION

It is a familiar fact that for a variable period, in normal cases not exceeding one week, the majority of infants lose weight after birth. This is a phenomenon which is very generally observed after the birth of animals.[1] In the case of man it is usually attributed to the fact that for the first few days succeeding birth the child receives little or no nutriment.[2] That this is probably not the only factor involved, however, is shown by the fact that the post-natal loss of weight is usually much greater when the child is excessively large[3] and also by the fact that it occurs even in young guinea-pigs, which are born in such an adult condition that they are capable of feeding themselves entirely by the fourth day. It must be admitted, however, that the power of these animals to nourish themselves at such an early date assists them to overcome a large part of the post-natal retardation of growth, for the retardation is relatively slight in guinea-pigs and frequently leads to an actual *loss* of weight only in the male.[4]

[1] Wo. Ostwald: Vorträge und Aufsätze ueber Entwicklungsmech. herausgeg. v. Wilh. Roux, Heft 5, 1908; J. Marion Read: Univ. of Calif. Publ. Zoology, 9 (1912), p. 341; Arch. f. Entwicklungsmech, 35 (1912), p. 708.

[2] P. Budin: The Nursling, trans. by Maloney, London, 1907, p. 74; J. W. Williams: Obstetrics, New York, 1912, p. 359.

[3] J. W. Williams: *loc. cit.*, p. 359.

[4] C. S. Minot: Journal of Physiology, 12 (1891), p. 97; J. Marion Read: Univ. of Calif. Publ. Zoology, 9 (1912), p. 341.

In the preceding article of this series,[5] I have presented a number of data concerning the weight of infants at birth after varying periods of gestation, derived from the records of "The Queen's Home," a maternity hospital in Adelaide, South Australia. In this institution the infants, whose mothers belong to the laboring and lower artisan classes, are weighed at birth and again upon discharge at from 13 to 15 days. Recently the practice has been instituted of also weighing the infants at one week after delivery, but only about one-third of the records which were placed at my disposal included the results of this weighing. My data concerning the weights of these infants at one week after birth are therefore less extensive than those which concern the weights at birth and at two weeks. They are, however, sufficiently numerous to permit the formation of certain conclusions which throw some light upon the origin of the post-natal loss of weight and the nature of the phenomena which succeed it.

The infants born at "The Queen's Home" are fed by the mother when this is feasible, six hours after birth and thereafter every four hours. A little water is given if needed, and milk diluted to one-fourth if the mother's milk is insufficient.

The data enumerated in this as in the preceding article concern only those infants which are the fruit of confinements which were, so far as could be ascertained, normal.

2. THE POST-NATAL LOSS OF WEIGHT

The following tables (1 and 2) exhibit the relationship between the post-natal loss of weight and the length of the period of gestation, the length of the period being estimated from the onset of the last menstruation and those cases excluded in which the infant weighed less at birth than the average weight of infants born thirty days previously or more than the average of infants born 30 days later.[6] Periods lying between 265 and 275 days in length are recorded as periods of 270 days, periods falling upon the limiting date separating two classes (e.g. 275

[5] T. Brailsford Robertson: American Journ. of Physiology.

[6] Cf. the preceding article of this series: *loc. cit.*

days) being included in both classes (e.g. the 270 and 280 day classes).

TABLE 1

Males

PERIOD OF GESTATION IN DAYS	NUMBER OF INFANTS	AVERAGE WEIGHT IN OUNCES	AVERAGE WEIGHT OF SAME INFANTS AT BIRTH	AVERAGE LOSS (−) OR GAIN (+) OF WEIGHT IN OUNCES
260	5	106	109	−3
270	9	114	119	−5
280	20	119	125	−6
290	14	137	141	−4

TABLE 2

Females

PERIOD OF GESTATION IN DAYS	NUMBER OF INFANTS	AVERAGE WEIGHT IN OUNCES	AVERAGE WEIGHT OF SAME INFANTS AT BIRTH	AVERAGE LOSS (−) OR GAIN (+) OF WEIGHT IN OUNCES
260	3	98	97	+1
270	9	110	110	±0
280	28	118	119	−1
290	21	119	125	−6
300	6	119	122	−3
310	2	127	132	−5

The average weights of the above infants at birth differ somewhat from those recorded in my previous communication because the number of infants of any one class is so small that their average weight at birth does not represent the true average for the class.

It will be seen that these data display no very clear correlation between the magnitude of the post-natal loss of weight and the length of the period of gestation preceding birth although there appears to be a certain tendency for infants born at the later periods to lose more heavily than those born after the briefer periods of gestation. This, as we shall see, is attributable to the fact that the infants born at the later periods are heavier and therefore larger than the infants born at the earlier periods.

The following tables (3 and 4) exhibit the relationship between the post-natal loss of weight and the weight of the infant at birth, all infants weighing for example, between 115 and 125

ounces at birth being regarded as having weighed 120 ounces at birth. Infants of which the weight at birth fell upon a limiting weight separating two weight-classes (e.g. 115 ounces) being included in both classes (e.g. the 110 ounce and 120 ounce classes).

TABLE 3

Males

WEIGHT AT BIRTH IN OUNCES	NUMBER OF INFANTS	WEIGHT AT ONE WEEK AFTER BIRTH	LOSS (−) OR GAIN (+) IN OUNCES
80	1	91	+11
90	3	86	− 4
100	6	104	+ 4
110	10	108	− 2
120	12	117	− 3
130	9	128	− 2
140	12	132	− 8
150	3	144	− 6
160	3	150	−10
170	1	160	−10

TABLE 4

Females

WEIGHT AT BIRTH IN OUNCES	NUMBER OF INFANTS	WEIGHT AT ONE WEEK AFTER BIRTH	LOSS (−) OR GAIN (+) IN OUNCES
80	3	77	− 3
90	5	94	+ 4
100	7	105	+ 5
110	17	108	− 2
120	19	118	− 2
130	17	125	− 5
140	6	129	−11
150	2	138	−12

It will be seen that there is a very clear correlation between the magnitude of the post-natal loss of weight and the weight (and, therefore; presumably the *size*) of the infant at birth. The infants weighing over 130 ounces at birth suffer especially severely, while infants weighing less than 110 ounces at birth, so far from losing weight during the first week after birth, fre-

quently gain considerably. From this it would appear legitimate to infer that *mechanical shock during delivery* is an important factor in determining the post-natal loss of weight.

The average weight at one week after birth of all the male infants (=57) born after periods of gestation lying between 245 and 325 days[7] was 121.4 ounces; the average weight of South Australian male infants at birth[8] is 127.3 ounces. Hence the average observed loss of weight during the first week after birth of South Australian male infants is 5.9 ounces or 4.6 per cent of their weight at birth.

The average weight at one week after birth of all the female infants (=79) born after periods of gestation lying between 235 and 325 days[9] was 115.0 ounces; the average weight of South Australian female infants at birth is 121.2 ounces. Hence the average observed loss of weight during the first week after birth of South Australian female infants is 6.2 ounces or 5.4 per cent of their weight at birth.

From these figures it would appear that the growth of female infants is more retarded by birth than that of male infants. That this is not really the case, however, is shown by the following considerations:

It must be recollected that the above figures do not represent the whole of the loss of weight due to birth. At the time of birth the infant is growing rapidly and if it were not for the shock, nutritional and mechanical, of birth the infant would *increase* considerably in weight during the first week of post-natal life. The *observed* loss of weight is therefore not the *actual* loss of weight. We may estimate the actual loss of weight to within a very close approximation, by the following method:

In the preceding article of this series I have shown that the

[7] Thus excluding the periods of gestation eliminated by Chauvenet's criterion as being probably pathological or otherwise abnormal. Cf. preceding article: *loc. cit.*

[8] Cf. the preceding article of this series: *loc. cit.*

[9] Thus excluding the periods of gestation eliminated by Chauvenet's criterion as being probably pathological or otherwise abnormal. Cf. preceding article: *loc. cit.*

latter part of the pre-natal and the first 9 months of the post-natal growth of South Australian male infants may be represented very accurately by the formula:

$$\log_{10}\frac{x}{341.5-x} = 0.136\,(t-1.66) \quad \ldots\ldots\ldots\ldots (1)$$

where x is the weight of the infant and t is the time, measured in months of 30 days, which has elapsed since birth.[10] Now at one week $t = \frac{7}{30} = 0.23$. Hence by putting $t = 0.23$ in the above formula we can estimate what South Australian male infants would weigh at one week after birth if it were not for the retardation of growth and loss of weight due to birth. In this way we find that at one week after birth South Australian males *should* weigh 133.1 ounces. They actually do weigh, as we have seen, 121.4 ounces. The *actual* loss due to the nutritional and mechanical shock of birth is therefore 11.7 ounces or 9.2 per cent of the weight at birth.

The formula which similarly represents the growth of South Australian female infants is:

$$\log_{10}\frac{x}{350-x} = 0.111\,(t-2.47) \quad \ldots\ldots\ldots\ldots (2)$$

and from it we find that at one week after birth South Australian females *should* weigh 126.2 ounces. They actually do weigh 115.0 ounces. The *actual* loss due to birth is therefore 11.2 ounces, which is 9.2 per cent of the weight at birth. Hence males and females suffer an *equal* retardation of growth as a result of the nutritional and mechanical shock of birth.

Since heavy infants suffer a greater post-natal loss of weight than light infants we should expect the *variability* in weight of infants to *decrease* during the first week succeeding birth, since the heavier infants tend to approximate more closely in weight to the light infants. This could only be the case, however, if

[10] Weights at periods antedating birth may of course be estimated by substituting negative values of t in the above formula equal in magnitude to the number (or fraction) of months by which the given periods antedate birth.

the variability of the loss itself were equal to, less than, or not greatly in excess of the variability in weight of the infants, for otherwise a very highly variable effect of the shock of birth might conceivably lead to an *increase* in the variability of the infants.

The variability of any quantity determined in a series of observations is measured in terms of the "standard deviation" and the *percentage* variability is given by the percentage ratio of the standard deviation to the mean magnitude of the quantity. The percentage variability is the maximum deviation from the mean which 68.27 per cent of the measurements may be expected to display.[11]

As I have shown in the preceding article the "standard deviation" of the weights of South Australian male infants at birth is 18.2 ounces and the variability is 14.3 per cent. I find that the standard deviation of the weights of South Australian male infants at one week after birth is 17.9 ounces and the variability is 14.7 per cent. The standard deviation of the weights of South Australian female infants at birth is 17.6 ounces and the variability is 14.5 per cent; while at one week after birth the standard deviation is 13.6 ounces and the variability is 11.9 per cent.

It is evident that, as might be anticipated, the post-natal loss of weight is accompanied by a decrease in the variability of the weight of *female* infants. In male however, infants, no such decrease but on the contrary a slight *increase* in variability accompanies the post-natal loss of weight. Evidently, therefore, the *variability of the effect of birth upon males is very considerably greater than the variability of its effect upon females.* The greater variability of the effect of adverse influences upon male infants is very probably correlated with the very much greater infantile mortality which prevails among males than among females,[12] since a greater variability of effect implies a more frequent overstepping of physiological limits.

[11] Cf. C. B. Davenport: Statistical Methods, 2d ed., New York, 1904, p. 16.

[12] According to the Commonwealth Statistician's Official Year Book for 1914, pp. 145 and 172 the ratio of the male to the female death-rate in Australia for death occurring less than 1 week after birth is 139 to 100.

3. THE GAIN IN WEIGHT DURING THE SECOND AND SUBSEQUENT WEEKS AFTER BIRTH

During the second week of post-natal life there is a marked gain in weight which not only makes good the loss of weight during the first week, but considerably exceeds it. The average weight at two weeks after birth of all of the male infants ($=203$) born after periods of gestation lying between 245 and 325 days was 130.6 ounces; hence (cf. above) the average gain over the weight at birth at the end of two weeks of post-natal life is 3.3 ounces. The average weight at two weeks after birth of all of the female infants ($=233$) born after periods of gestation lying between 235 and 325 days was 124.2 ounces, the average gain over the weight at birth being 3.1 ounces.

These gains, however, although they more than serve to make up the *observed* losses of weight due to birth, do not entirely compensate for the *actual* loss of weight due to birth (i.e., the observed loss plus the *gain* in weight which the infant would have displayed had it not been for the retardation due to growth). This may be shown by putting $t = 0.47$ ($=$ two weeks) in the formulae (1) and (2) and computing with their aid the weights which the infants should display at two weeks after birth. In this way we find that at two weeks after birth South Australian male infants *should* weigh 139.3 ounces, while they actually *do* weigh 130.6 ounces. Hence the retardation of growth due to birth is, after two weeks of extrauterine growth, 8.7 ounces or 6.8 per cent of the weight at birth. Similarly we find that at two weeks after birth South Australian female infants *should* weigh 131.2 ounces, whereas they actually *do* weigh 124.2 ounces. Hence the retardation of growth due to birth is, after two weeks of extrauterine growth, 7.0 ounces or 5.8 per cent of the weight at birth.

Although the gain in weight during the second week of extrauterine life is not sufficient to entirely make up the loss due to birth, it will be noted that it *partially* does so, for the loss of weight in males due to birth is 11.7 ounces at one week and only 8.7 ounces at two weeks. In other words the effect of birth does

not result in a *permanent* subnormality in the weight of the infant because the loss of weight due to birth is made up by a *compensatory overgrowth* (i.e., growth in excess of the normal increment corresponding to the given age and period) which amounts during the second week, in males, to 3.0 ounces. This compensatory overgrowth is even more pronounced in females, amounting to no less than 4.2 ounces during the second week of extrauterine life. Evidently females recover more rapidly than males from the inhibitive effects of birth upon their growth, a fact which doubtless is correlated with the greater tolerance of adverse conditions and the lesser variability of the post-natal loss which female infants display.

The compensatory acceleration of growth during the second week may be shown in another way. From equation (1) it may readily be computed that between the end of the first and the end of the second weeks of extrauterine life the increment of weight in males, if their growth proceeded at the normal velocity indicated by preceding and succeeding weights, should be 6.2 ounces. The observed increment is no less than 9.2 ounces. Similarly the increment during the second week in females should be 5.0 ounces and actually is 9.2 ounces. Evidently the rate of growth in males is accelerated 48 per cent and that of females no less than 84 per cent.

By the end of the first month of extrauterine life this compensatory process has entirely made good the loss of weight due to birth, so that at one month the observed weight of male infants is "normal," that is to say, lies exactly upon the continuous curved line which represents preceding and succeeding growth.[13] In the case of South Australian female infants there would appear, from my previously-published data, to be even over-compensation, since the observed mean weight at one month is decidedly "supernormal."

From these facts it would appear that the normal weight of a growing organism at any given age represents a true dynamic equilibrium, any disturbance of which is rectified by internal regulation, just as a gyroscope restores equilibrium to a mass

[13] Cf. preceding article of this series: Amer. Journ. of Physiology.

which has been displaced from its "normal" position through the action of an external force. If the induced displacement be too great the inertia of the gyroscope may be insufficient to restore the mass to its original position and analogously we may infer that if the induced sub- or super-normality of the weight of an organism, induced by the action of an adverse environment, exceeds a certain "physiological limit," the internal regulatory processes may be impotent to retrieve the damage to the economy of the organism.

This "internal regulation" of the process of tissue growth is also very well illustrated by the phenomena of tissue-regeneration whether following a wound, when the neighboring tissues are especially stimulated to growth, or following a more generally dispersed loss of tissue-material, as in the marked nitrogen-retention following the wasting of fever or of starvation. The remarkable acceleration of tissue-accretion which succeeds partial starvation upon returning to a full diet is very well illustrated by the following experiment:

Eight young white mice, varying in age between 52 and 123 days, which had hitherto been permitted free access to food and water, were found to weigh an average of 19.0 grams. They were then deprived of food for 27 hours and of water for the last four hours of this period. On again weighing, their average weight was found to be only 15.3 grams. The loss due to 27 hours of starvation was therefore 3.7 grams or 20 per cent of their original weight. They were now given free access to rolled barley, dried bread and water. One hour later they were weighed again and it was found that one-fourth (25 per cent) of the above loss had already been made good; this represents, doubtless, the weight of the contents of the alimentary canal after a full meal. After 21 hours no less than 87 per cent of the loss had been made good, the average weight being now 18.5 grams. Had this rate of increment of weight been continued these mice, already two-thirds grown, would have doubled their weight in five or six days!

This phenomenon of internal compensation is, of course, entirely in harmony with the view which I have expressed else-

where,[14] that the growth of an organism is regulated by and is the expression of a series of underlying chemical reactions which are of such a nature (autocatalytic) that they produce their own catalysors.

The variability of the weight of male infants at two weeks of age is 14.0 per cent, while that of females is 14.3 per cent. Evidently the extent of the compensatory overgrowth is just as variable, in both sexes, as the weight at birth, i.e., as the preceding "normal" growth. Hence the diminished variability of female infants, which results from the post-natal loss of weight during the first week, is lost during the succeeding week owing to the variability of the normal and compensatory increments during that period.

4. SUMMARY

1. Data are presented concerning the post-natal loss of weight and the compensatory acceleration of growth which succeeds it in South Australian infants, the fruit of normal confinements.

2. There is no decided correlation between the magnitude of the post-natal loss of weight during the first week of extra-uterine life and the length of the period of gestation which preceded birth. There is, however, some tendency for the infants which are born after longer periods of gestation to lose somewhat more heavily than those which are born after briefer periods of gestation. This is because the latter infants are lighter and smaller.

3. There is a very clear correlation between the magnitude of the post-natal loss of weight and the weight (and therefore size) of the infant at birth. Infants weighing over 130 ounces (3680 grams) at birth suffer especially severely, while infants weighing less than 110 ounces (3120 grams), so far from losing weight during the first week after birth, frequently gain considerably. From this it would appear legitimate to infer that *mechanical shock during delivery* is an important, although not the only factor in determining the post-natal loss of weight.

[14] T. Brailsford Robertson: Arch. f. Entwicklungsmech., 25 (1908), p. 581; 26 (1908), p. 108; 37 (1913), p. 497.

4. Male and female infants suffer an equal retardation of growth due to birth, the actual loss of weight (= observed loss plus gain which would otherwise have been made) after one week being 9.2 per cent of the weight at birth.

5. The variability of the effect of birth upon males is very considerably greater than the variability of its effect upon females. This is probably correlated with the greater infantile mortality of males during the first weeks of extrauterine life, since a greater variability of effect implies a more frequent overstepping of "physiological limits."

6. The post-natal loss of weight is followed by a compensatory acceleration of growth which is more pronounced in females than in males. By the end of the second week of extrauterine life 48 per cent of the loss in males and 84 per cent of the loss in females has been made good by means of compensatory overgrowth. By the end of the first month the entire loss has been made good.

7. The normal weight of a growing organism at any given age represents a true dynamic equilibrium, any disturbance of which is rectified by internal compensation.

8. The following is a summary of the quantitative data reported herein:

South Australian Infants

	MALES		FEMALES	
	Weight in ounces	Variability	Weight in ounces	Variability
		per cent		*per cent*
At birth	127.3	14.3	121.2	14.5
At 1 week	121.4	14.7	115.0	11.9
At 2 weeks	130.6	14.0	124.2	14.3

THE VASCULAR TONE AND THE DISTRIBUTION OF THE BLOOD IN SURGICAL SHOCK

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INTRODUCTION

We present in this paper a study of the vascular tone and of the distribution of the blood in the condition known as "surgical shock." There is no explicit definition of this term, but for practical purposes in connection with the present investigation, it may be assumed to mean a low arterial blood pressure of such duration that recovery is impossible. Our observations, on dogs, were continued until death intervened. We had therefore the condition as defined. It is apparent to anyone who has studied surgical shock that the condition is a complex one, and it follows that the several factors concerned may establish themselves independently of one another or in varying sequence. Our data clearly support that part of the conception advanced by Henderson[1] that shock is associated with loss of venous tone. This loss of venous tone may initiate a train of events fatal in their outcome, such as the failure of the heart to fill in diastole (Henderson), but the significance of the loss of venous tone relative to other possible factors contributing to shock is beyond the scope of the present paper.

EXPERIMENTAL

Of the numerous experiments performed in approaching the general subject of surgical shock, we desire to emphasize three types particularly, (a) observations of the vena caval and portal

[1] Henderson: American Journal of Physiology, 1908, xxi, 155.

venous pressures in conjunction with the arterial pressure; (b) observations of the changes in the weight of an isolated loop of gut and (c) observations on the perfusion rate in isolated vascular beds.

(a). *Observations on the venous pressure.* In a few of the experiments, the anaesthetic was morphia and chloretone; in the others morphia and ether. Effort was made to maintain anaesthesia uniformly. Shock was hastened in some cases by exposure of the viscera to air, and in a few cases by manipulation of the exposed viscera, but in general the plan followed was to allow the animal to lie undisturbed after the operation, except for the procedures incidental to the regular observations of the venous pressure. The latter was accomplished by passing a long cannula filled with sodium citrate solution toward the vena cava by way of the external jugular or femoral vein; or into the portal vein by way of one of the branches.

The *vena cava pressure* was observed in thirteen experiments. They all showed a progressive fall in pressure. As contrasted with changes in the portal pressure these experiments exhibited a rather steady fall in venous pressure which was not associated with changes which occurred in the descent of the arterial pressure curve.

The *portal venous pressure* was observed in seven experiments. The pressure falls much less regularly in this system than it does in the vena cava as noted above. It sometimes shows a progressive fall which parallels an even drop in arterial pressure but in general it is quite irregular, in the earlier stages of the experiment rising and falling with the fall and rise of the arterial pressure. Indeed in the majority of these experiments on the portal pressure we felt that we could roughly determine the point of onset of shock by noting the time at which the inverse relationship between the portal and arterial pressure changed to a parallel relationship. Again it may maintain itself for several hours quite independently of the arterial pressure. But sooner or later it falls and this fall in such instances is indicative of approaching death. We incline to take the view from these experiments therefore that the vascular

changes in shock are chiefly associated with the splanchnic area.

In the experiments such as those described in which graphic records of the venous pressure were obtained there was observed a terminal rise of venous pressure coincident with the death of the animal. This rise is presumably dependent on the ultimate failure of the arterial tone. Mann[2] who has recently reported the observation that the femoral venous pressure is low in shock, noted that in this condition, section of the sciatic nerve produced "an immediate and decided increase in the pressure of the femoral vein." This may therefore be regarded as contributing evidence that arterial tone is at least not wholly lost in shock.

The venous pressure follows the downward course well recognized in the case of the arterial pressure. The evidence advanced by Porter[3] and by Seelig and Lyon[4] that the peripheral arterial resistance is increased in shock in conjunction with these results strongly suggests, as predicated by Henderson, that the blood is stagnated in the dilated veins. This idea is further supported by the observation that the smaller mesenteric veins stand out conspicuously, a fact also noted by Mann. In an effort to illuminate this point, we placed an isolated loop of gut with nerves and vascular supply intact on a balance and observed the results.

(b) *Observation on the weight of a loop of gut.* In two such experiments the anaesthesia was morphia and ether. A loop of the small intestine about 30 cm. long was isolated and wrapped loosely in rubber tissue. The abdominal wall was closed sufficiently to hold back the rest of the viscera, and the animal was suspended vertically. The stalk of the loop of gut permitted the latter to extend far enough to lie on the pan of a delicate balance which was counter-weighted and described its movements on a smoked drum. The stalk of gut, unprotected by rubber tissue was kept moist and soft with an occasional spray

[2] Mann: Johns Hopkins Hospital Bulletin, 1914, xxv, 205.
[3] Porter and Quinby: American Journal of Physiology, 1908, xx, 500.
[4] Seelig and Lyon: Journal American Medical Association, 1908, lii, 45.

of salt solution. In order that the stalk should not be under tension as the loop of gut changed in weight the counter-weight was frequently altered to maintain a small excursion of the recording lever.

TABLE 1

Heart-rate, respiratory rate, arterial blood pressure and weight of loop of gut (relative) in surgical shock

TIME	HEART-RATE	RESPIRATORY RATE	ARTERIAL PRESSURE	WEIGHT OF GUT (RELATIVE-)*
11.00	60		70	19.0
15	60	28	70	19.0
30	60	28	76	17.5
45	92	22	96	13.5
12.00	122	20	104	9.0
15	134	18	112	10.5
30	134	20	108	6.0
45	164	20	110	4.0
1.00	170	18	100	5.0
15	174	16	110	2.5
30	172	14	114	2.0
45	176	16	116	1.25
2.00	170	16	116	1.0
15	166	16	118	1.0
30	170	14	120	0.5
45	176	16	124	2.0
3.00	186	20	112	7.0
15				4.5
30	188	13	120	5.5
45	188	12	118	6.0
4.00	188	12	120	14.0
15	166	36	114	14.0
30	170	40	100	15.0
45	170	36	92	15.5
5.00	142	56	84	18.5
15	134	50	70	20.0
30	124	42	60	19.5
45	120	20	45	20.5

* Figures used represent movement of recording lever in millimeters.

In the first experiment (table 1), the weight values for the loop of gut are relative only. The loop was little heavier at the end than at the beginning of the experiment. The vessels at the beginning may have been paralysed as the result of manipulation. However this may be, the gut decreased steadily in

weight for four hours. The arterial pressure rose sharply for two hours and then more slowly for six hours. Toward the end of the latter period the weight of gut varied considerably, and then began a progressive increase which roughly paralled the fall in arterial pressure.

In the second experiment (fig. 1) the plotted curve representing the changes in weight of the loop of gut gives these changes in absolute value. It will be noted that the experiment

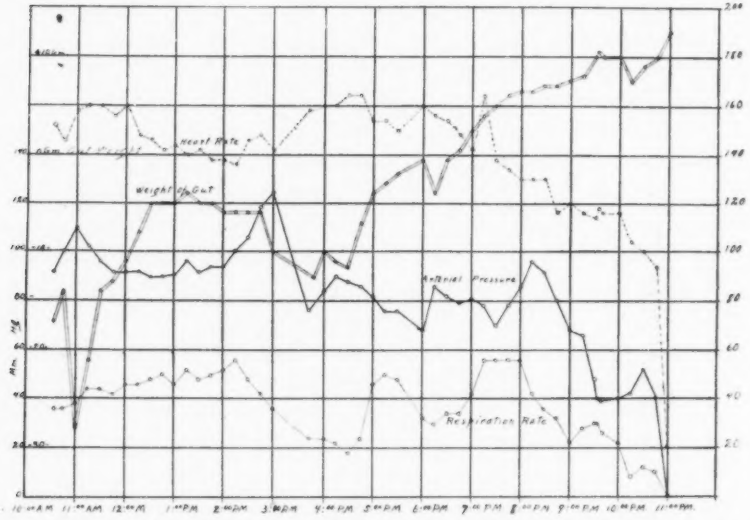

Fig. 1. To show the change in weight of an isolated loop of gut with nerves and blood supply intact in surgical shock. The divisions of the abscissae represent time in hours. The divisions of the ordinates represent (a) 20 mm. Hg. for arterial pressure, (b) 20 heart beats and respiratory movements and (c) 5 gm. for changes in weight of the loop of gut.

lasted over a period of twelve and one-half hours, during which time the loop of gut increased in weight over 30 grams. In the first four and one-half hours the arterial pressure was well maintained, although the loop of gut had increased in weight. At the end of this period the loop of gut lost in weight at a time roughly coincident with the break in the arterial pressure. Thereafter the weight of gut steadily increased while the arterial pressure fell until the end.

Objection may be offered to the conclusions drawn from such experiments on the ground that an oedematous condition of the tissues might be a cause of the increase in weight observed. This objection cannot be entirely excluded but the general trend of the curves and the appearance of the intestinal loop at the end of the experiments were such as to indicate that oedema played no part in the increase in weight recorded.

The pulse and respiratory rates recorded appear unrelated to the onset of the terminal changes in the arterial and venous pressures, as noted by previous observers. In the curve described by the changes in weight of the loop of gut, a progressive fall precedes the break in arterial pressure, a circumstance which suggests a final effort on the part of the venous portal system to meet the approaching crisis. When this system fails, the arterial pressure begins to fall in spite of an increased heart rate, and the weight of gut increases indicating stagnation of the circulating blood. This stagnation is further indicated by the markedly "venous" color of the shed blood, and by an increased respiratory effort.

These experiments indicate that there is vascular dilatation in the splanchnic area. The results of Porter and of Seelig and Lyon, above alluded to, by exclusion would place this dilatation on the venous side. Porter based his conclusions on the percentile rise and fall of arterial pressure following stimulation of sensory nerves. Seelig and Lyon observed the rate of outflow from the femoral vein before and after section of the sciatic nerve comparing the outflow on one side before shock, with that of the other after shock. Quite recently Seelig and Joseph[5] have demonstrated that if in a rabbit, which has previously had the vascular nerves to one ear destroyed and which is thrown into shock, the arterial pressure be raised by occluding the abdominal aorta the operated ear becomes engorged while the unoperated ear remains normal in appearance. If, after this control, the second ear was operated and the arterial pressure raised both ears become engorged. The conclusion is

[5] Seelig and Joseph: Proceedings Society for Experimental Biology and Medicine, 1914, xii, 49.

obvious that the vascular tone in the second ear was maintained even in shock.

(c) *Observations on the perfusion rate in isolated vascular beds.* We sought with a technical procedure not hitherto employed to investigate the condition of arterial tone in shock. Our results confirm the findings of others on this point and call for brief mention only. It seemed to us possible that, if the pressure was maintained constant, the rate of flow through a given vascular area might be greater in shock than before the condition was established. It was however necessary to choose areas in which the blood flow should be normal except during the observations. This requirement was established in the case of the hind leg, the kidneys and that portion of the large intestine supplied by the inferior mesenteric artery. For the kidneys inflow and outflow cannulae were laid in the aorta and vena cava distal to the renal branches all minor vessels being tied. Loose ligatures placed above the renal branches permitted the isolation of the organs during the perfusion. For the intestine the inflow was managed in a like manner the outflow being received from a vein caudal to the area under investigation. The loose ligature for the vein in this case was laid about the portal proximal to the area to be isolated. For the leg the femoral artery and vein of the opposite side received the cannulae, other vascular branches being tied, and the loose ligatures for use during isolation were placed above the aortic and vena caval bifurcations. In all ten experiments were performed, using both Ringer's solution and defibrinated blood for perfusate. The perfusion pressure was maintained constant. The temperature of the perfusate was likewise maintained constant except in one experiment in which the temperature was allowed to fall as the temperature of the animal fell. Of these experiments six were performed upon the leg and two each on the kidneys and intestine. In but one of these experiments (leg) was the outflow increased after shock was established. In one of the experiments on the intestine the nerves running to the part were severed after shock was established and resulted in a decided increase in the rate of outflow.

CONCLUSIONS

1. Both the systemic and portal venous pressures fall in shock.

2. The weight of an isolated loop of gut is increased in shock, a fact interpreted to mean loss of local vascular tone. This loss of tone may be arterial or venous or both. Our evidence indicates loss of venous tone which would predicate failure of the veno-pressor mechanism and a stagnation of venous blood.

3. Perfusion of vascular areas, temporarily isolated for observation, shows a decreased rate of flow in shock.

SOME CHARACTERISTICS OF VASOMOTOR REFLEXES

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The original purpose of the experiments to be described in this paper was to test the effect upon blood-pressure of stimulation applied to each of two afferent paths and to both simultaneously. It was thus closely analogous to the purpose of Camis (1) in his study of the reflex contractions of a selected skeletal muscle. He found that in many instances a more extensive contraction could be produced by stimulating two or three afferent paths at once than could possibly be secured through one alone. A degree of diffuseness and a lack of unity in the motor centres was inferred. It seemed a matter of interest to make similar trials for the vasomotor mechanism; to see whether greater effects upon arterial pressure could be produced through the excitation of a large number of afferent fibres than could be obtained with a smaller number. As the work proceeded other matters, not foreseen at the outset, claimed a share of our attention.

After we had pursued our task for some time we discovered that W. T. Porter, in 1908 (2), had projected a similar study. He had suggested that an investigation of this kind would throw light on the comparative effects of stimulating small and large areas of the skin by temperature changes or otherwise. We wish to give all the credit that is due to Dr. Porter but the lapse of time and the unconsciousness of any invasion of his field, so far as we were at first concerned, appeared to us to warrant the continuance of our work.

Many years ago Grützner and Heidenhain (3) were impressed by their observations that localized stimulation of the skin

is less efficient in causing pressor reactions than stimulation applied to large areas, even when the former is intense and the latter mild in character. Unfortunately, they did not attend to the fact that they were stimulating receptors instead of nerve-fibres. A mode of stimulation which may seem to be gentle may be in reality highly effective in generating impulses when it is brought to bear upon appropriate end-organs. This is probably the case with blowing upon the skin, a measure often employed by Grützner and Heidenhain. From a purely physical standpoint this is a mild application but biologically it is a potent one since there are specific endings ready to respond to it and to transmit impulses along the afferent channels of the mechanism for temperature regulation.

The salient facts regarding vasomotor phenomena attending the stimulation of afferent nerves may now be recalled. The effect on the blood-pressure varies with the strength of the excitation. With weak shocks there is a fall which becomes gradually more marked as the strength of the stimuli is increased but soon lessens again and is exchanged for a rise when a certain rather definite stimulation strength is exceeded. Martin and Lacey (4), using the quantitative method developed by the former, have found that this "threshold of the pressor reaction" is passed when the value of the shocks is rated at about 280 Z units in terms of the Martin system (5). With additional increase of stimulation the elevation of the blood-pressure becomes more and more marked through a long range. The account given is valid for vagotomized animals.

When we compare the effect of stimulating two nerve-paths at the same time with that of exciting each by itself we have to face a problem of summation. But in the large literature of this subject the reference is usually to the successive application of two or more stimuli at one place (6). The summation with which we had to deal was a simultaneous variety although there must have been present in it the element of successive shocks. The central machinery was played upon by both streams of impulses. When we undertook to observe the influence of weak currents such as would cause a reflex fall of blood-pressure it

was evident that the interpretation of records must be difficult. Summation of effect might appear as an increased *fall* of pressure or, if the two weak applications should prove equivalent to one much stronger, a reversal of effect might be witnessed or, possibly, there might be no disturbance at all if the pressor and depressor tendencies should chance to balance. These sources of confusion were anticipated but it seemed reasonable to expect that if the stimulation applied to each of the two nerves was sufficiently strong to produce a pressor effect, then the simultaneous employment of two such excitations should give results of a clear character.

It may be suggested that to stimulate two afferent nerves at the same time may be merely equivalent to the stimulation of one of them with shocks of a higher frequency. But Martin and Lacey (4) have found that the interruption of the primary current can be made to take place at widely varying rates without affecting the extent of the vasomotor change resulting from the stimulation of a single afferent path.

Method. The animals used were cats, anesthetized by ether or urethane. The carotid pressure was recorded by a mercury manometer. Different nerves were chosen for stimulation, sometimes symmetrical pairs, sometimes two on the same side of the body, and sometimes two unsymmetrically located but on opposite sides of the axis. Sherrington electrodes, or a modified form devised by Martin, were placed on the nerves and every precaution against needless exposure was taken.

The primary current (usually 0.1 ampere) supplied to Martin's calibrated coil was interrupted by the vulcanite-mercury key, described in other papers (7). The key was worked by a crank on the shaft from a large pulley belted to an electric motor. Both makes and breaks were allowed to take effect in order to minimize polarization.

The question may be asked whether anything akin to polarization actually occurs, under the best conditions, when a segment of nerve is subjected to an alternating current for a considerable time. We believe that under the conditions of our experiments there is no appreciable impairment of irritability and

no diminution in the effectiveness of the shocks from any such local cause. Our opinion is based on the following type of experiment. Two pairs of Sherrington electrodes were placed on the same nerve. The peripheral pair were used to apply prolonged stimulation. When the vasomotor response waned the stimulation was brought to bear upon the fresh segment of the nerve between the first point of application and the centre. With comparable strengths of current it was found that the shift did not add to the efficiency of the stimuli.

We will now pass to the routine procedure. By manipulating plugs the secondary currents could be sent through either pair of electrodes or both in series. It will be evident that when the current is sent through segments of two nerves in series, instead of one, an increased resistance is encountered and the stimulating potency at a given point is diminished. This difficulty we overcame by the following arrangement. A Wheatstone bridge could be employed at any moment to determine the resistance of the secondary with either nerve in circuit. The same resistance could then be provided by means of a rheostat and the current made to traverse the box when not directed through the nerve. Thus when one nerve was stimulated the current was tempered by an artificial resistance equal to that of the other nerve and when both were in circuit the resistance was removed.

At the outset we need to know the typical features of the reflex changes in blood-pressure when only one nerve is stimulated. The fall of pressure produced by weak stimulation is mild in degree, rarely over 10 per cent, and transient, recovery taking place in spite of continued excitation. It has been ascribed to a reflex mediated by the vaso-dilators (8). Pressor responses are much more variable. Sometimes the tracing shows a peak and a steady decline within the period of stimulation, as though fatigue of some sort were manifested by the mechanism. Sometimes the record has a plateau character, giving little impression of fatigue and showing a prompt subsidence when stimulation ceases. There is a third possibility, that a plateau formed under the influence of afferent currents

may be continued with little sagging in the after-period. In such cases the blood-pressure keeps for a long time a new and high level. We have called this a "boosting reaction" and we cannot yet recognize the conditions which favor its occurrence.

A curve given by Sherrington (9) shows a pressor reaction continuing far beyond the period of stimulation, with a slow decline to the original level. Such instances, which we have often seen, suggest the possibility that adrenalin may have been released as a result of the stimulation. But we cannot attribute to adrenalin a rise of pressure which does not at all outlast the stimulation period.

In some of our earlier trials we were able to demonstrate a moderate degree of summation even when we did not employ compensatory resistances. That is to say, a current carried through segments of two nerves in series and tempered by their combined resistance was more effective than when applied to only one nerve even though in this latter case the lowered resistance insured a considerable increase of stimulation. Naturally enough, we were able to confirm the fact of summation when the omission of either nerve from the circuit was compensated for by introducing an appropriate resistance. But it is fair to say that the extent of possible summation, when two nerves are stimulated instead of one, is quite limited. (Figures.)

Another matter eventually proved to be of rather more interest than the primary question of summation. This was the possibility of establishing a pressor reaction by stimulating one nerve and then prolonging or even intensifying it by shifting the exciting current to another nerve. Again and again we found that we could overcome the flagging of blood-pressure when the first application ceased to be effective by introducing a second in place of the first, that is, by substitution instead of summation. The work of Forbes (10) may be referred to as throwing light upon this phenomenon. His studies, like those of Camis, were upon reflex contractions of skeletal muscles.

Forbes showed that when the reflex response of a single muscle can no longer be secured by stimulating the path which originally produced it, a renewed contraction may be counted on if

another afferent path is substituted. The inference is that the fatigue which is manifested when the reflex at first disappears is due to the blocking of a line of approach to the centre. Presumably it is a case of rising synaptic resistance. It is assumed that the nerve-cells which are conceived to form the centre

Fig. 1. Summation of depressor effects. Nos. 11 and 12 show the slight reaction obtained by stimulating each of two nerves, No. 13 the more marked response when both are stimulated at once, the shocks remaining of the same intensity as before.

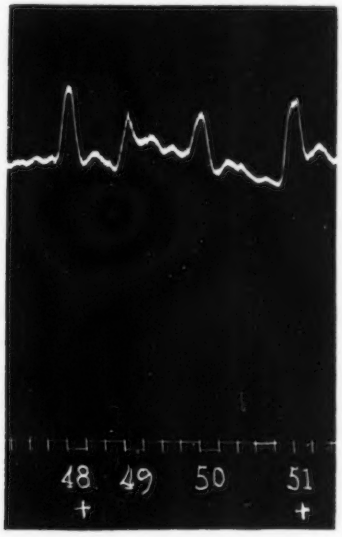

Fig. 2. Summation of pressor effects. Nos. 48 and 51 show the effect of strongly stimulating two nerves at once, Nos. 49 and 50 record the individual responses to the stimulation of each of the two nerves alone. The stimuli were of equivalent strength throughout.

and the efferent paths are the same, first and last. Therefore, the primary fatigue cannot be of the motor apparatus nor of the presiding neurons; it must be sought on the afferent side.

The same conclusion is suggested when a failing pressor reaction is reinforced by shifting the stimulation to a second nerve.

Here again, if we assume that the same muscular elements are concerned each time the pressure is raised, and that the centre has such a degree of unity that all its cells are involved in each pressor reflex, we shall be led to believe that fatigue of particular approaches is to be reckoned with. An alternative view will be presented later.

One characteristic of the vasomotor mechanism is the rapid recovery from fatigue. If we evoke a pressor response which nearly passes away in the course of 30 seconds or a minute of continued stimulation, we can duplicate it with entire success after an interval of rest equal to, or even shorter than, these periods. It is to be noted that continuous stimulation after the blood-pressure has fallen back to its original level is not likely to revive the pressor reaction. Yet, after an intermission of a minute or less, the resumption of stimulation (the intensity being as before) may reproduce the original elevation of pressure. In other words, the continued excitation has prevented recovery from fatigue at the centre even after it has ceased to produce peripheral effects. Quick fatigue and quick recuperation are more naturally associated with synapses than with other features of the system.

Noting that a very short period of rest restores the capacity for full pressor reactions, we were interested to find out whether the alternate stimulation of two afferent paths would give a better sustained elevation of blood-pressure than the continued stimulation of one for a long period. The shifting was sometimes effected once in 30 seconds, sometimes once a minute, and occasionally at longer intervals. The resistances of the nerves were known and, unless the two were nearly equal, the stimulation of either one was through a circuit containing a resistance equal to that of the other nerve.

Another method of assuring comparable stimulation of two paths was also employed. This was to find for the two nerves two positions of the secondary coil with which equal pressor effects could be secured and then to use with each nerve the appropriate strength of stimulation.

As we accumulated results we viewed them with increasing

dissatisfaction. It appeared in some cases that the adoption of a new path of approach did not at all reinforce the failing reaction. In other instances the reinforcement was most striking. It was only when we reviewed a large mass of these data that they began to assort themselves in an orderly way. All the observations were found to be consistent with the following principle: when a pressor effect, secured through stimulation of given path, declines, little is gained by transferring the application to a *neighboring* nerve, but a renewal of the pressor reaction is generally to be counted upon when the stimulation is shifted to a *remote* part of the body. The "remote" locality may be symmetrical to the first or far removed from it on the same side. When the choice of nerves is fortunate a judiciously managed alternation of the two may hold the blood-pressure at a well sustained elevation for many minutes.

An experiment may be cited to illustrate the facts just stated. A cat under urethane was vagotomized and two nerves of the right leg were prepared. They were the popliteal and peroneal. The left peroneal was also made ready for stimulation. After preliminary trials to find a suitable strength of current the right popliteal was strongly stimulated for 6 minutes. The pressor plateau was well sustained. After 2 minutes rest the two nerves in the right leg were subjected to alternate stimulation, shifting after each 90 seconds, for $7\frac{1}{2}$ minutes. The popliteal received the same stimulation as before; the peroneal a current previously determined to give a pressor response of the same order as its fellow. The plateau produced in the record by alternate stimulation nowhere exceeded the height of that secured from the popliteal alone and repeatedly sagged when the change from one nerve to the other was made.

For comparison, the left peroneal was stimulated for 6 minutes. This gave a considerable rise of pressure at first and then a decline to a plateau which was held to the end. After a rest of one minute this nerve and its companion on the right—a "remote nerve"—were stimulated alternately, changing once in 90 seconds. The height of the previous plateau was twice surpassed in $7\frac{1}{2}$ minutes while each shift brought reinforcement, never sagging.

How shall we interpret the facts? There seem to be two possibilities. (1) If the vasomotor centre is assumed to have strict unity the reinforcement obtained through employing a fresh afferent path of excitation in place of one which has ceased to be effective may be explained along the lines of Forbes' conception. But if remote nerves must be selected to secure positive results we shall have to conclude that neighboring nerves utilize a common approach to the centre. (2) We may incline to the view of Camis, assuming that the centre is not strictly integral in action. If this is the case it may be inferred that the stimulation of two nerves near together affects the vessels in a field which is but little different from that which either one commands. Fatigue may really be on the side of the effectors. The renewed effect produced by stimulating a distant nerve may thus be due to the contraction of blood-vessels not previously involved. But if the vasomotor centre were much given to partial reactions we might well look for strongly summated effects when the stimulation of two nerves remote from one another was simultaneous.

SUMMARY

1. Stimulation of two afferent paths at the same time has often a more marked vasomotor effect than the stimulation of either path alone with an equivalent strength of current. The degree of summation is only moderate.

2. When a pressor reaction, secured by stimulating a given nerve, declines it can often be renewed by shifting the stimulation to a second nerve. The renewal is much more to be relied on when the second nerve is distant from the first than when it is near.

3. The superior reinforcing power of a distant nerve may be accounted for on the theory that its afferent connections with the centre are unimpaired by previous use (the Forbes principle) or we may suppose that it has access to a fraction of the central mechanism not previously stimulated and through this to a fresh set of vessels.

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A STUDY OF THE CAUSES OF RESPIRATORY CHANGE OF HEART RATE

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INTRODUCTORY

Of all the factors the sum total of whose effects results in the respiratory wave of blood pressure, a factor of great interest, and as yet not fully understood, is that of the respiratory change of heart rate. The chief explanations of the change in heart rate may be grouped under two headings, namely *reflex* (Einbrodt, Hering, Luciani) and *automatic* (L. Traube, Fredericq).

These explanations are so pertinent to the matter about to be presented that it seems necessary to restate them and the evidence upon which they were based.

Luciani[1] who still holds to Einbrodt's view, explicitly speaks of the act as reflex, saying that he takes the respiratory change of heart rate "to be the effect of a reflex rhythmical excitation of the bulbar centre of the cardiac vagi during the expiratory acts." From this statement one must suppose that the expiratory act sets up afferent impulses that are reflected back to the heart from the vagal centre, thus causing slowing of rate. A perusal of Einbrodt's own paper does not make this so clear. He may have meant that the activity of the expiratory centre in the bulb influenced the vagal centre, increasing its tone and thus causing slowing of the heart rate.

Both Einbrodt and Luciani are agreed that it is the expiratory act that (reflexly or automatically) increases vagal tone.

Hering[2] based his conclusion upon an experiment in which he observed in the dog respiratory change of heart rate during

[1] Luciani, L.: Human Physiology, London, 1911, i, p. 435.

[2] Hering, E.: Wiener Sitzungsberichte, 1871, lxiv, p. 333.

artificial inflation of the lungs as well as during normal breathing. The conclusion was that the mechanical stimulation of the pulmonary terminals of afferent vago-sympathetic fibres reflexly stimulated the cardiac accelerator centre, and thus increased heart rate during inspiration.

But L. Traube[3] and Fredericq[4] showed another possibility. The former observed respiratory change of heart rate both in dogs deeply curarized and with sectioned cervical cord, the latter in dogs with patent chest walls and lungs collapsed. The conclusion was that respiratory change of heart rate was brought about by "an automatic rhythm common to the respiratory and cardio-motor centres." The quotation is from Fredericq's[4] classical work, in which much was done to clarify the relations of these centres one to another. Nevertheless Fredericq's statement leaves a certain vagueness as to the locus and mechanism of the stimulus which leads to respiratory change of heart rate. For this reason it is necessary to paraphase his statements and if possible put them in more modern phraseology.

In the first place Fredericq is convinced that respiratory change of heart rate may not be a true reflex; the original stimulus need not arise in the periphery. His experiment shows that beautifully. Its origin must be in the bulb itself. In the medulla there is an *automatic* rhythmical mechanism which is common to the respiratory, the vaso-motor and the cardio-motor centres. It is thus that rhythmical tonus waves, emanating synchronously with the respirations from the vaso-motor centre, may produce respiratory waves in the blood pressure by rhythmically changing the calibre of the blood vessels (true Traube-Hering waves). It is thus that tonus rhythms emanating from the cardio-motor centre synchronously with the rhythmic activity of the respiratory centre may produce respiratory waves of another character, waves of changing heart rate. It is during *expiration* that both the vaso-motor and cardio-motor centres receive their maximum influence from this "rhythme automatique." And so it happens that often no

[3] Traube, L.: Gesammelte Beiträge, 1865, i, p. 390. Quoted from Fredericq.
[4] Fredericq, L.: Archiv de Biologie, 1882, iii, p. 55.

respiratory wave obtains in the blood pressure. For the action of this "rhythme automatique" upon the circulatory centres have opposing effects. If the vaso-motor centre be more excitable than that of the cardio-motor, the result may be the paradoxical wave of rising pressure during cardiac retardation, of falling pressure during cardiac acceleration. Again if the cardio-motor centre be the more irritable, one observes a respiratory wave of falling pressure with cardiac retardation, of rising pressure with cardiac acceleration, the opposing vaso-motor effect being entirely masked by the greater effect of changing heart rate.

The conceptions of both Luciani and Fredericq are the same then in so far as they attribute *the prime agency leading to change of heart rate to be directly connected with the expiratory act.* The difference in the two authors is that the one regards the phenomenon as a true reflex, the other as an automatic influence, possibly of some intermediary rhythmical process coexisting in the medulla. In more modern literature physiologists are inclined to regard this intermediary process as superfluous. The same effect is had by the possible spreading of the activity of one centre to neighboring centres. This process has long been spoken of as *irradiation.*

Turning to clinical literature one finds views of greater variance. On the whole, however, the question seems to have received slight attention from clinical men. How great the variance of views is is indicated by Mackenzie[5] when he says that many of his fellow practitioners regard respiratory change of heart rate as a pathological symptom of a condition requiring treatment, but that he himself after many years' observation came to regard it as "a youthful type of irregularity," and finally as an indication of "a healthy heart." This author makes no considerable attempt to explain the phenomenon, aside from the statement that "the slow respiration induces an irregular action of the heart due to stimulation of the sino-auricular node. The condition is due to vagus stimulation

[5] Mackenzie, James: Diseases of the Heart, 3rd edition, London, 1913, pp. 55, 184, 187.

. . . ," and again, "the vagal effect produces the irregularity." From which one is left to infer that vagal centre tonus rises and falls with the respirations. As to a cause of the rise and fall of vagal tonus nothing is said.

NEW OBSERVATIONS

It may be stated at this point that the physiological evidence on the nature of the mechanism producing respiratory change of heart rate, is all in favor of the *automatic* or *irradiational* hypothesis and against the *reflex* hypothesis, so far as that implies origin of stimulation at the periphery.

I. On the mammal

During routine work confirmation of this view is often observed, but rarely does it appear in such clear and irrefutable form as in the record here reproduced.

The record, however, contains more than a refutation of the *reflex* hypothesis of respiratory change of heart rate. *The record contains very clear evidence that it is not the expiratory act but rather the inspiratory act (at most the whole respiratory act)* of the respiratory centre that gives rise to the influences leading to change of heart rate. Furthermore the influence is not to increase vagal tone, but to decrease or remove it. Other evidence will be submitted to show that the *expiratory* act neither reflexly nor automatically can be the usual cause of respiratory change of heart rate. And this then is at once the justification not only of its publication but also of the foregoing somewhat detailed exposition of older and well known work.

a. Vagal tone produced by electrical stimulation. The conditions under which the observations were made were somewhat as follows (see fig. 1):

The animal, a dog, is the usual experimental preparation under morphia and ether, tracheotomized with ether bottle attached. A mercury manometer is attached in one carotid. Both vagi have been exposed, one of which, the right, has been divided; the other has been left, as the rest of the animal, intact.

Fig. 1.—From the record of the experiment of May 19, 1914, reduced to ⅓ of the original. The figure is to be read from right to left. The trace at bottom marks zero blood pressure and also serves as stimulation signal. The next trace is time in seconds. The trace next to the top trace is the blood pressure (mercury manometer) trace. The topmost trace marks the respirations; the upstroke indicates inspiration. Scratch marks on the record show that the writing tip of the respiratory pen stood from 5 to 7 mm. to the right of the writing tip of the blood pressure pen in the original.

Stimulation of the central stump of the divided vagus gave the remarkable results which are shown in the portion of the kymograph record here reproduced (see fig. 1). One reads the figure from right to left. Scratch marks appearing on the record near the portion which is here exhibited, show that the writing tips of respiratory and blood pressure pens deviated from the vertical from 5 to 7 mm., the respiratory point being to the right of the blood pressure point. This correction is used in placing the scratch marks in the figure, synchronous points being indicated by corresponding numerals. The upstroke of the respiration lever marks the inspiratory movement. In the record the lowest trace marks simultaneously zero pressure and the points of stimulation. The time mark at the top is in seconds. The beginning of the record in the figure (right side) shows the pulse rate to be about 116, the respiratory rate 20. The blood pressure trace shows a well marked respiratory wave. The mean pressure is about 128 mm. Hg.

Faradic stimulation is then applied to the central stump of the divided vagus for a period of about 22 seconds.

The events that follow are:

1. A prompt inhibition of the respiration at the end of the expiratory phase.

2. A slow rise of mean blood pressure for about the first 13 seconds of the stimulation, when a pressure of 140 mm. has been reached.

3. At this point the stimulation begins to affect the cardio-inhibitory centre which, through the intact vagus, slows the heart rate in an unusually smooth and regular fashion. The new rate is about 44 beats per minute.

4. The mean pressure in this last stage at first falls slightly below normal and then remains constant at about 100 mm. Hg.

5. The respiratory movements continue in perfect inhibition for some time after removal of the stimulation; the blood pressure trace with its greatly slowed pulse rate, as well as the respiratory trace, shows no sign of a respiratory wave.

6. This picture continues for some 32 seconds, when the blood pressure trace suddenly shows great waves which turn out to be unmistakable respiratory waves.

7. *At the time of the appearance of the first of these respiratory waves, no sign of mechanical act of respiration can be found on the respiratory trace.* By the time the second wave appears, the respiration lever shows the smallest indication of respiratory movement. From this point on, the pneumograph movements slowly and gradually become augmented in size until they reach normal dimensions.

8. Now a remarkable thing appears. As the respiratory movement becomes augmented, the size of the respiratory waves just as gradually and slowly become smaller until (it would be too long a trace to reproduce) they are again of the dimension and character of the respiratory waves found in the blood pressure record just before the stimulation was applied to the vagus.

If one compares the respiratory trace (noting scratch marks) with the blood pressure trace carefully, one becomes convinced that in this part of the record the *slowing of the rate occurs during the pause between the expiratory and following inspiratory acts. The acceleration on the other hand begins sharply with the inspiratory act* and continues to the end of the expiratory act.

With the end of expiration the inhibition, or great retardation, again sets in promptly.

The sudden appearance of the respiratory waves upon the smooth blood pressure trace at a point *just before* the respirations are resumed, can only be interpreted as follows:

1. The respiratory centre just recovering from the inhibition produced by faradization is throwing out impulses to the inspiratory mechanism. These impulses are ineffective, but the energy of the active centre is powerful enough (one imagines the activity to arise as rhythmical explosions) to interfere with the exaggerated tone of the vagal centre brought on by the previous electrical excitation.

The inspiratory explosion being over, its action upon the vagal centre ceases and the latter's exaggerated tonus is free to express itself again in the marked cardiac retardation that one observes in the record.

2. As there were, on account of the electrically elicited inhibition of respiratory centres, no actual respiratory movements,

it is clear that there could have been no intra-thoracic or intra-peritoneal changes of pressure, and hence also no peripheral stimulation of afferent vagal terminals. *The first respiratory blood pressure waves therefore* (as in Fredericq's dog with patent chest walls and collapsed lungs) *must be referred to a central causative agent.*

3. The fact that the respiratory change of heart rate diminishes as the inspiratory movements increase (not shown entirely in the figure), on the other hand, is still additional evidence against Hering's *reflex* hypothesis, namely that mechanical stimulation of afferent terminals in the pulmonary vagi reflexly gives rise to the phenomena of respiratory change of heart rate.

4. Inspecting the section of the record not all shown in figure 1, one notes that it is the inspiratory and not the expiratory movements that are being augmented. The pneumograph lever drops back always to what is clearly a constant expiratory base line. Furthermore the expiratory movements are of the passive kind; there is no evidence that they involve either nervous or muscular energy. The activity of the expiratory centre at this point may therefore be considered as nil.

5. The fact that the respiratory waves gradually diminish with diminishing change of heart rate is clearly explained by supposing that the hyperactivity, or exaggerated tone of the vagal centre, brought on by the electrical excitation, gradually subsided, as in experience it always does. The inspiratory centre thus no longer influences the vagal centre so markedly, not because the inspiratory centre is less active (it apparently is much more active), but because the vagal centre is under less tone and, therefore, has less tone to be removed.

To sum up briefly, the record here reproduced contains new and unmistakable objective proof that the cardio-motor centre may be directly influenced by its neighboring respiratory centre. The evidence of Fredericq which originally led to this belief was obtained upon an animal with open thorax and collapsed lungs. The evidence in the case here reported is obtained upon an animal with chest walls intact, but with the respirations tempo-

rarily thrown in a state of inhibition, and the cardiac vagal centre simultaneously thrown into a state of increased tone. Rhythmical change of heart rate suddenly appears and directly thereafter a return also of the respiratory movements. The time relations of the blood pressure wave, produced by the rhythmical change of heart rate, and the reviving respiratory movements are such that one concludes that the change of heart rate was initiated by the reviving activity of the respiratory centre before the latter was able to cause respiratory movements. The effect of the activity of the respiratory centre was to remove the vagal tone and thus allow cardiac acceleration, cardiac retardation taking place again during the respiratory pauses.

These time relations also indicate that it is most probably not the activity of the *expiratory* centre that *stimulates* the vagal centre, but rather the activity of the *inspiratory* centre which *depresses* the vagal centre, or possibly excites the hypothetical cardiac accelerator centre.

b. Vagal tone produced by epinephrin. The above case of increased tone of vagal centre was produced by faradization of the vagal nerve. The same effect may be produced by intravenous injection of epinephrin. Here again, as is shown in figure 2, acceleration of heart rate promptly sets in with the beginning of inspiratory movement; retardation of heart rate begins at the end of expiration and continues during the respiratory pause. As in the case of electrical stimulation, so also in the case of epinephrin injection, the preliminary condition to vagatonie is increased blood pressure; the respirations may or may not be arrested. In figure 2 the epinephrin given was not sufficient to interfere with respirations in any noticeable degree. This however may be accomplished by increasing the amount of epinephrin.

Indeed Mr. M. C. Sosman in the course of an investigation which he is carrying out in this laboratory has been able to reproduce all the effects obtained by faradic stimulation (as shown in fig. 1) by epinephrin injection alone. His experiment and results were as follows:

A dog of about 6 kgm. weight under morphia and ether was given intravenously about 5 mgm. of partially oxidized epinephrin. At once the usual rise of pressure appeared then very marked slowing of heart rate. The blood pressure however remained high in spite of the great slowing of heart rate and the respiration was completely arrested at the end of 70 seconds.

At the end of 118 seconds with the respirations still inhibited rhythmical change of heart rate set in which condition continues for 51 seconds longer, when shallow inspiratory movements begin. The periods of these respiratory movements have the same time as the rhythmical waves of changing heart rate.

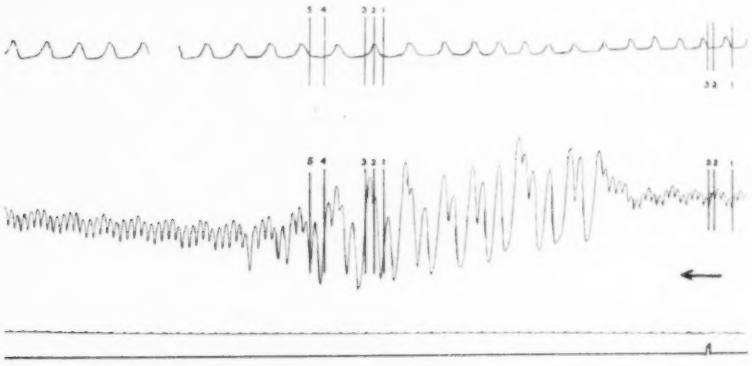

Fig. 2.—From the record of the experiment of April 24, 1914, reduced to ⅓ of the original. The trace marks are to be read in same order as in figure 1. In this record the scratch marks were all on same vertical. At the signal mark 3 cc. of weak solution of epinephrin was intravenously injected. The dog was under morphia and ether and both vagi were intact.

Here again it appears that the activity of the respiratory centre may effect the vagal centre long before it does the respiratory mechanism itself.

II. On man

The above section has only dealt with the experimental animal. Do the same relations hold between the bulbar centres

in man? Respiratory change of heart rate in man has been long a matter of observation. The general rule has been that cardiac acceleration accompanies inspiration, while retardation accompanies expiration.

If one asks a patient in whom respiratory change of heart rate is present to hold his breath at the end of a normal expiration, or rather to allow the chest walls to pause in a perfectly passive condition, *the retarded character of the heart rate continues.* This retardation cannot now be attributed to the action of the expiratory centre, for that is in a state of quiescence.

Examination of such a subject leads to only one conclusion, namely that the heart is under the influence of a constant vagal tone which for that condition constitutes the fundamental rate for the heart. *This fundamental rate undergoes change (acceleration) only when the influence of the reviving activity of the inspiratory centre reaches the vagal centre.* The effect is, then, inhibition of the vagal centre, hence inspiratory acceleration.

If the vagal tone be removed by drugs or fever (as Fredericq showed) respiratory change of heart rate drops out, either because the endings of their nerves or the cardio-motor centres themselves have lost their exquisite state of irritability, or inner activity.

It is important to pause at this point to consider other reasons that point against the possibility of the expiratory act producing retardation.

1. In quiet normal breathing it is the inspiratory phase which is the active phase of the movement complex; the expiratory phase is regarded generally as being perfectly passive and requires no muscular tension, no innervation.[6]

2. In the same normal breathing it is the inspiratory act which is inhibited by afferent pulmonary impulses in the vago-sympathetic trunks; the expiratory centre under this condition receives no inhibition—there is no activity to inhibit. On the contrary if further expiration is required, stimulation, not inhibition, of the expiratory centre begins at this point of the respiratory cycle.

[6] See however, Howell, W. H.: Textbook of Physiology, 5th edition, 1913, p. 685.

3. Furthermore it is an inspiratory not an expiratory act which terminates a period of apnoea.

4. Our general knowledge of the agents that bring on vagotonie, i.e. excitation of the vagal centres, would lead to the view that normal activity of other neighboring centres is not one of them, rather is such activity productive of a depression or removal of vagotonie.[7]

5. Cardiac vagotonie is not specially a rhythmic condition. Our conception of it is a *constant* and not an *intermittent* condition of the vagal centre. In case of respiratory change of heart rate it is more likely, then, that the activity of the inspiratory centre may with its rhythmical action also depress its neighboring cardiac vagal centre, that is, momentarily remove the tonus and *thus rhythmically remove the excessive slowing of the heart rate, hence cause cardiac acceleration.*

6. In his exhaustive work on the accelerator mechanism of the heart, Reid Hunt[8] it will be remembered came to the conclusion that "almost all cases of rapid heart action are due to a diminution of the tonic activity of the cardio-inhibitory centre."

SUMMARY

1. Respiratory change of pulse rate in experimental animals (dogs) is described, consisting of a marked acceleration during the whole of the respiratory movements, and a marked retardation during the pause between the respirations.

2. The blood pressure changes thus produced consist of inspiratory rise lasting to the end of expiration, and a fall lasting during the pause between the respirations.

3. This respiratory wave of blood pressure was produced (a) by electrical stimulation of the central stump of one vagus, the other vagus being left intact; (b) by intravenous injection of epinephrin.

[7] Meltzer, S.: Archiv f. Anat. u. Physiologie, 1883, p. 221. It is here shown that cardiac acceleration accompanies the act of swallowing, which the author explains as an inhibition of vagatonie.

[8] Hunt, Reid: Amer. Journal of Physiology, 1899, ii, 435.

4. When the "respiratory" waves were produced electrically their appearance on the blood pressure trace was preceded by prolonged respiratory inhibition. Contrary to expectation it was not the respiratory *movements* which were first revived but the respiratory *blood pressure waves themselves.*

5. The time relations of the reviving respiratory movements, which appeared soon after the blood pressure waves made their appearance, were such that one and one conclusion only could be made, namely that it was the activity of the reviving *inspiratory* centre which, though too feeble or meeting too much resistance, to innervate the appropriate respiratory mechanisms to movement, still by some means (irradiation of energy, automatic rhythm, Fredericq) was able to influence its neighboring vagal centre in such a way as to remove from it the excessive tone under which it for some time previously had been laboring. The removal of the vagal tone appears to have been accomplished by an actual depression of the inhibitory centre.

6. Similarly, when cardiac slowing is produced by injection of epinephrin, the time relations of the respiratory waves in the blood pressure to those of the respiratory movements are such as to point again to the activity of the inspiratory centre as being the initial agency in the production of the respiratory wave, and in the same manner, that is by inhibiting the vagal centre.

7. It is further pointed out that in many cases respiratory change of heart rate in man may be likewise explained. The probable cause in such cases is the existence of excessive vagal tone proceeding from a highly sensitive vagal centre. This heightened tone is intermittently depressed or removed during the activity of the inspiratory centre. So soon as the *inspiratory* activity ceases (during expiration or the respiratory pause) the tone of the vagal centre is free again to act causing the familiar expiratory retardation of the heart.

CONCLUSION

The thesis here presented the author believes is new in so far as

(a) It gives proof, of a different character from that given by previous workers, showing that the cause of respiratory change of heart rate is in the spinal bulb and not in any peripheral mechanism; is an automatic and not a reflex mechanism.

(b) It opposes the view that this cause is in the activity of the expiratory centre.

(c) It gives positive proof that the agent lies rather in the activity of the inspiratory centre.

(d) It is inclined to regard the mechanism as rather a depression of vagal centre than a stimulation of the hypothetical accelerator centre.

ELECTRICAL STUDIES IN MAMMALIAN REFLEXES

I. The Flexion Reflex

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CONTENTS

INTRODUCTION

Although the mammalian spinal reflexes have been studied exhaustively with the myograph method by Sherrington,[2] Graham Brown[3] and others, we have found no record of researches in which the modern quick-acting electrical recording devices have been applied to their analysis through the action currents

[1] We wish to thank Mr. McKeen Cattell for assistance in the last five experiments.

[2] Sherrington: Integrative Action of the Nervous System. 1906; Proc. Roy. Soc., vol. 81, 1909, p. 249; Journal of Physiology, vol. 40, 1910, p. 28; Quart. Journ. Exp. Physiol., vol. 6, 1913, p. 252; Journal of Physiology, vol. 47, 1913, p. 196.

[3] Graham Brown: Quart. Journ. Exp. Physiol., vol. 7, 1914, pp. 197–418, etc.

of the motor nerves. The action currents of human muscles in voluntary contraction and on electrical stimulation of their motor nerves have been led off through the skin and recorded with the string galvanometer by Piper[4] and by Garten.[5] The same method has been used by Snyder[6] and by Hoffmann[7] in the study of the knee jerk and ankle jerk, whose reflex nature seems to be accepted by a majority of investigators. Jolly[8] has applied the same method to the study of reflex time in the case of rabbit, cat and man. Piper[9] has also examined the action currents of muscles in the turtle under reflex stimulation. Reflexes in the frog have been examined through the action currents in the muscles by Buchanan[10] with the capillary electrometer and by Beritoff[11] with the string galvanometer.

The action currents of the extensor muscles in the decerebrate cat have been examined by Buytendyk[12] with the string galvanometer, and an attempt is mentioned by him to observe the action current of the sciatic nerve under reflex stimulation. Foa[13] reported a successful observation of this sort at Vienna in 1910, but no details are given as to the animal used, the method, or the results.

With the exception of the last two experiments, we find no case in which the various records obtained from muscles have been compared with any record obtained directly from motor nerves under similar conditions. Gotch and Horsley,[14] in 1891, published an extensive study of the electrical disturbances in

[4] Piper: Electrophysiologie menschlicher Muskeln. Berlin. 1912; Pflügers Archiv, vol. 119, 1907, p. 301; ibid., vol. 127, 1909, p. 474, ibid., vol. 129, 1909, p. 145; Zeitschrift für Biologie, vol. 50, 1908, p. 393, p. 504.

[5] Garten: Zeitschrift für Biologie, vol. 52, 1909, p. 534.

[6] Snyder: American Journal of Physiology, vol. 26, 1910, p. 474.

[7] Hoffmann: Arch. für Physiologie, 1910, p. 223.

[8] Jolly: Quart. Journ. Exp. Physiol., vol. 4, 1911, p. 67.

[9] Piper: Arch. für Physiol., 1910, p. 207.

[10] Buchanan: Journal of Physiol., vol. 27, 1901, p. 95; Quart. Journal of Experimental Physiol., vol. 5, 1912, p. 91.

[11] Beritoff: Zeitschrift für Biologie, vol. 62, 1913, p. 125.

[12] Buytendyk: Zeitschrift für Biologie, vol. 59, 1912, p. 36.

[13] Foa: Zentralblatt für Physiologie, vol. 24, 1910, p. 792.

[14] Gotch and Horsley: Phil. Trans. London, vol. 182, 1891, p. 267.

various parts of the mammalian nervous system with tetanic stimuli applied to various points. The apparatus available at that time was not capable of recording rapid and minute electrical changes with the accuracy now obtainable with the capillary electrometer made by Lucas's[15] method or with the string galvanometer. Furthermore, their attention was devoted to tracing the various conducting paths rather than to analyzing reflex responses with reference to their time relations. Einthoven[16] has studied the action currents of the vagus nerve under various conditions with the string galvanometer, and Dittler[17] has made a similar study of the phrenic nerve. This method, however, has apparently not been applied to the mammalian spinal reflexes which are so well known from the point of view of the myograph.

Buchanan[18] has presented evidence tending to show that the rhythm found in the action currents of muscles in voluntary contraction may be an intrinsic rhythm of muscle independent of any rhythm of impulses in the motor nerve supplying it. Dittler infers (vide supra) that the rhythm in muscle exactly corresponds with that in the motor nerve. As yet no evidence on either side seems to us wholly conclusive. Because of this it seems desirable to use the action currents of the motor nerves themselves where possible, as an index of central nervous action, especially when dealing with rapid rhythm. In view of the importance of rhythm in the activity of the motor centres, there seems to be a useful field for the employment of a method of recording which will eliminate the possibility of confusion arising from any natural periodicity of the muscle or the recording apparatus itself. Furthermore, in certain investigations, such as those dealing with the effects of drugs on the nervous system, it is especially desirable to use a method in which possible changes in the muscles cannot confuse the results. Motor nerves also

[15] Lucas: Journal of Physiology, vol. 37, 1908, Proc. Physiol. Soc., p. xxviii.

[16] Einthoven: Quart. Journ. Exp. Physiol., vol. 1, 1908, p. 243.

[17] Dittler: Pflüger's Archiv., vol. 131, 1910, p. 581. Cf. also ibid., vol. 130, 1909, p. 400.

[18] Buchanan: Journal of Physiology, vol. 27, 1901, p. 95; Quart. Journal Exp. Physiol., vol. 1, 1908, p. 211.

present certain advantages over muscles for this sort of study in that they can be isolated for considerable lengths with but little disturbance to their physiological state and with absolute certainty that no shift of contact with electrodes can confuse the result by changing the demarcation current.

With these considerations in view, this study of the flexion reflex in the decerebrate mammal has been made. This reflex was chosen as being the simplest and most regular reflex obtainable in response to the simplest stimulus, the single induction shock. In the course of the experiments certain facts have appeared which have an interesting bearing on the problem of the spread of reflexes and the theory of graded synaptic resistance. The discussion of these facts and the problem they present will be reserved for a later paper. The present paper deals with a description of the general properties of the flexion reflex in the cat as recorded by the action current in the motor nerve, and a comparison of these records with those similarly obtained from the muscle innervated by the same nerve under the same conditions of stimulation.

METHOD

A. Electrical recording apparatus

We have used throughout these experiments an Einthoven string galvanometer furnished by the Cambridge Scientific Instrument Co. of Cambridge, England. During the greater part of the work this was provided with magnet coils connected in series and excited by the 220-volt direct current from the local power plant. In the last few experiments this was replaced by a low resistance coil in two parts connected in parallel, and excited by eight Edison storage cells (type B-6) arranged in series. This furnishes a magnetic field almost identical with that of the other coil, and has the advantages of dependable steadiness and complete insulation from other circuits. When the first coil was in use and excited from the 220-volt circuit, the iron core of the magnet was regularly put to earth. Since in the Cambridge galvanometer the upper end of the string is metallically connected with the iron core, this procedure, of

course, involves putting the string to earth. With the low voltage coil this was not done except in special cases.

Three strings have been employed in the galvanometer in the course of the present investigation. The first of these, "String C," is of platinum and has an average diameter of 3μ and a resistance of approximately 5000Ω. This string was prepared from Wollaston wire by Dr. H. C. Hayes of the Physics Department at Harvard. It was used only in a few of the earlier experiments. The second, "String D," lent us by Dr. Hayes, was of silvered glass, made by the Cambridge Scientific Instrument Co., and had a dimaeter of 5μ and a resistance of about 1750Ω. This was used in the majority of the experiments. The third, "String E," was made by Dr. H. B. Williams of the College of Physicians and Surgeons of New York. It is of quartz silvered by the cathode spray method described by him.[19] It has a diameter of 1.5μ and a resistance of 16,100Ω.

With strings C and D the tension was in general adjusted at about the limit of periodicity. That is, when a resistance of the average magnitude found in the physiological circuit is connected in series with the string and the closure of a constant current recorded, the calibration curve thus obtained shows only a small over-shoot amounting to one or two per cent of the total excursion (e.g., figs. 5, 6 and 11). The tension at which this type of curve was obtained was about 62 per cent greater in the case of string D than with string C, for the inertia of the latter was greater and the air damping less. The time required for the string to reach the full magnitude of its excursion at a given tension varies according to the resistance in circuit on account of the electromagnetic damping. The resistance of the nerve under observation as included in the circuit usually lay between 15,000 and 40,000 ohms. With such resistance in circuit, string C would reach its final amplitude of excursion in about 15σ at the tension commonly used, while string D at the higher tension at which it was usually employed reached its full excursion in about 13 or 14σ. The magnification of the string which was constantly

[19] Williams: Physical Review, vol. 2, series 2, 1913, p. 402.

employed in these experiments was 580 diameters. With this magnification string C at the tension commonly employed gave an apparent excursion of 1 cm. with a current of 8×10^{-8} amp. The tension commonly employed with string D was such that 1 cm. measured 13×10^{-8} amp.

String E on account of its extreme lightness possessed a wider range of tensions which could be used without rendering it periodic. With a tension about two and one-half times as great as that used with string D and nearly four times as great as that used with string C and with resistances of 20,000 to 40,000 ohms in series, the overshoot was only of the same order as that commonly found in the calibration curves with the other strings, i.e., about 1.5 per cent. Moreover, at this tension the full magnitude of excursion on the make of a constant current was reached in about 4σ. At this tension, therefore, it was possible to obtain far more accurate records as regards time relations than was possible with either of the other strings. Where this was desired the tension mentioned (1 cm. = 31×10^{-8} amp.) was used. On the other hand, excursions in response to nerve action currents are small at this tension, and since even at slacker tensions the initial portion of the excursion is quicker than is obtainable with the heavier strings, a tension equal to or less than that used with string D was employed where it was desired to compare magnitudes of disturbance.

The galvanometer was mounted on a wooden stand built solidly against the outside stone wall of the building. This position was found to be remarkably free from vibration. The wires in the circuit which included the string, were all insulated and lead-sheathed, and the lead sheaths were grounded. All switches and resistances in circuit with the string were mounted on hard rubber blocks or porcelain bases to insulate them from the tables on which they stood. Figure 1 shows diagrammatically the arrangement of wires, etc., in connection with the string. From one terminal of the string (G) a wire is led to one end of a slide wire 1 metre long having 4.8 ohms resistance. This slide wire is connected in series with resistance box (R_1) and with an Edison cell through a pole-changing switch. The other ter-

minal of the string is led to one pole of a two-way, double-throw switch (*DS*) which connects the string either with the physiological preparation or with a substitution resistance (R_2) as desired. From the other pole of this switch a wire is led to the sliding contact on the slide wire. With this arrangement the resistance in R_1 is so adjusted that the fall of potential along the slide wire shall be 0.001 volt to 1 cm. or to 10 cm. or to any other convenient value. This makes it possible to introduce quickly into the circuit in series with the string and either the nerve or the substitution resistance any desired E.M.F. from 0.0001 volt or less to 0.1 volt in either direction; and the voltages so used are read directly from the meter scale without computation.

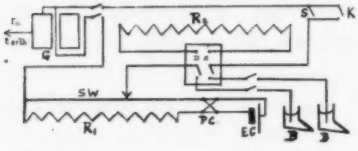


Fig. 1. Electrical connections. *G*, string galvanometer. *DS*, two way double-throw switch. *EC*, Edison storage cell. *PC*, pole-changing switch. *SW*, slide wire. R_1, resistance box to regulate compensating current. R_2, substitution resistance. *K*, spring contact key. *S*, knife blade switch. *B,B*, non-polarisable boot electrodes.

A simple spring contact key (*K*) is operated by hand for making calibration curves, while for permanent closure of the circuit a knife-blade switch (*S*) is arranged in parallel at the same point in the circuit. The make calibration curve is identical wherever the circuit is closed, since the excursion is always opposed by electro-magnetic damping. In Einthoven's constant current records the key is so placed that the return of the string following the break is also electro-magnetically damped. With our arrangement this is eliminated and the return is opposed only by air damping.[20] This method is sometimes useful when it is desired to show what part electro-magnetic damping plays in the record.

[20] Cf. Samojloff: Pflüger's Archiv., vol. 149, 1913, p. 492.

B. Optical system

In dealing with complex physiological preparations it has been deemed best to simplifiy as far as possible procedures incidental to recording, so that our attention should not be diverted from the physiological part of the experiment by the need of making adjustments. To this end a Nernst lamp has been used for illumination in place of the arc lamp which is generally employed in projection work. This glows indefinitely with absolute steadiness and without need of adjustment when once placed in position. Its intrinsic brilliancy is so much less than that of an arc lamp that it would not suffice for making photographic records at the required speed and magnification without far greater economy of light rays than is found in most projection systems. This has been achieved by introducing two cylindrical lenses

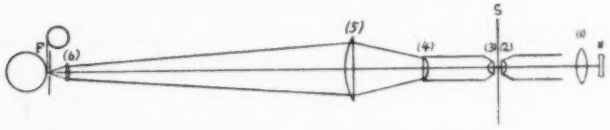


Fig. 2. Diagram of optical system. *N*, Nernst glower. (*1*), double convex lens. (*2*), condensing objective. *S*, string of galvanometer. (*3*), projecting objective. (*4*), ocular. (*5*), large plano-convex cylindrical lens. (*6*), small plano-convex cylindrical lens in camera. *F*, photographic film.

into the system. The general arrangement of lenses is indicated in figure 2. The Nernst filament is placed in a vertical position about 30 cm. away from the string. Close to the light is placed a 16 D double convex lens (1), and in the rear draw-tube of the galvanometer a 16 mm. objective (2) which serves as a condenser. These lenses and the light are so placed that an image of the Nernst filament is focused in the plane of the string and again at the plane of the recording surface, and their positions are further selected so that this latter image of the Nernst filament shall have the same width as the film. In this way the maximum available illumination is secured. In the front draw-tube are placed a 16 mm. Zeiss objective (3) and a Zeiss No. 8 compensating ocular (4) for projecting the image of the string. About 20 cm. in front

of the ocular, and mounted on a separate stand, is a large 6 D plano-convex cylindrical lens (5). In the receiving camera is a plano-convex cylindrical lens (6) of 4.9 cm. principal focal distance corresponding to that in other recording apparatus employed with the string galvanometer. Behind this lens is the recording film which travels in a vertical direction. The distance from the string to the film is 133 cm. Without the large cylindrical lens (5) the small one would only receive a small portion of the light emerging from the ocular, but with this lens properly placed practically all of the light is concentrated in a narrow horizontal beam falling on the smaller lens; this is, in turn, concentrated so that nearly all of it falls on the narrow slit in front of the film. With this double system it is impossible to obtain a sharp horizontal line of light from the smaller cylindrical lens as is commonly done in other recording apparatus, and it is necessary to rely for definition on a narrow slit in front of and as close as possible to the film. In our experiments the slit has been such that a band of light about 0.8 mm. wide falls on the film at a given instant. For very minute analyses involving exact time measurements this would not be satisfactory, but for the purposes of this research where time measurements more accurate than to 0.0005 second were not required the method has been efficient and especially convenient. The placing of these cylindrical lenses has been done empirically by shifting back and forth until the maximum illumination is found. In obtaining a sharp focus of the string it is essential that the axis of curvature of the big cylindrical lens (5) should be exactly parallel with the string (i.e., vertical), and to insure this a fine adjustment with rack and pinion is provided whereby this lens is rotated in its own plane about the optical axis till the best definition is obtained.

In the last four or five experiments an arc lamp was used for illumination. This made it possible to dispense with the large cylindrical lens and to make the light fall in a sharp line across the film. This rendered measurements of time more accurate than with the system just described.

C. Photographic recording apparatus

The recording camera was built around a Sandstrom electric kymograph; it was especially designed to record large numbers of observations in rapid succession and to work in daylight. For this purpose it has proved eminently satisfactory. The Sandstrom kymograph is driven by the power plant current and is provided with a governor which makes possible an approximately constant speed. It is also provided with an extensive series of gears by which at constant velocity of the motor a wide range of velocities of the drum is obtained.

The film is reeled off from a spool, around the kymograph drum and on to another spool in a separate receiving chamber. The velocity of the film is determined wholly by the kymograph drum against whose surface the film is pressed firmly by rubber rollers held in place by springs. The spool in the receiving chamber is turned by a spring clock-work device. The pull of this is adjusted merely to take up the slack of the film and is not made strong enough to modify the velocity imparted to it by the kymograph drum. The arrangement of these parts is shown in vertical section in figure 3.

The film used is $3\frac{1}{2}$-inch moving picture film supplied by the Eastman Kodak Co. in 50-foot rolls. It comes on simple wooden spools with holes drilled in the ends. In loading the camera the spool bearing the film is set up at *F* (fig. 3) in a frame in which its unwinding is opposed by a slight friction. From here it is led around the surface of the kymograph drum and out through an opening (*O*) by which it connects with the receiving chamber (*R*).

The kymograph is provided with a drum having a circumference of exactly 50 cm. In order to economize film and to render the camera compact a smaller brass drum was substituted for this. It has a circumference of 14.1 cm. and has flanges at the ends to keep the film from lateral excursion. It was found necessary to supplement these with guide plates between the feeding spool and the drum making it impossible for the film to ride up on the flanges and get jammed.

The drum is so placed that the film passes as close as possible behind the slit (*S*), and then with the least possible distance to traverse into the receiving chamber. The purpose of this chamber was to make it possible to remove for development the exposed portion of the film without having to dismount the whole camera and take it to the dark room. It was made, according to a plan suggested by Dr. E. S. Kilgore, of two concentric brass cylinders, one fitting close inside the other. The ends are closed by plates, each of which is fastened rigidly to one of the cylinders and has a hole in its centre for the shaft of the receiving spool inside to pass through. Large flanges at the ends of the receiving spool prevent any light which enters these holes from reaching the film. A lengthwise section through the chamber with the spool in place is shown in figure 4.

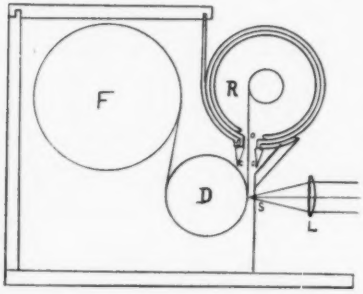


Fig. 3. Vertical section through recording camera. *F*, spool of film. *D*, kymograph drum. *O*, opening from camera to receiving chamber. *R*, receiving chamber. *C*,*C*, spring clips which close opening and grip the film when receiving chamber is removed. *S*, adjustable horizontal slit. *L*, cylindrical lens.

To admit the film a slit is cut lengthwise in each cylinder, and when the chamber is fitted to receive the film these are set to coincide with each other and with the opening (*O*, fig. 3) in the camera. Two lips fastened to the outer cylinder press open a pair of spring clips (*c*, *c*) at the opening, which when the receiving chamber is removed close on the protruding end of the film and prevent light from entering the camera. Before removal, the inner cylinder is rotated within the outer so that the slits no longer coincide and the film is held firmly as it enters between the overlapping portions of the cylinders. The chamber is then raised and the film cut between it and the camera. When thus closed, the receiving chamber has proved absolutely light tight.

When the receiving chamber is in place the shaft of the spool is connected by a disc coupling with the shaft of the spring device whereby slack is taken up and the film wound in as it leaves the drum.

The slit through which the light enters in front of the drum can be varied in width by fine adjustment screws. In front of the slit is a shutter which may be closed by hand when the apparatus is not in use. This is not found necessary as a rule for on account of the shape of the camera only about an inch of film can be fogged with the shutter left open. The position of the small cylindrical lens which is mounted in the camera in front of the slit is regulated by fine adjustment screws to give the best concentration of light.

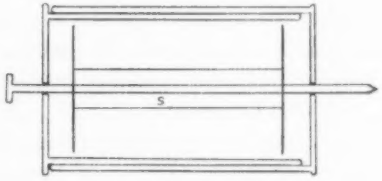


Fig. 4. Longitudinal section of receiving chamber showing receiving spool (*S*) within.

The kymograph is operated by setting the electric motor in motion, and when this has attained its full velocity, by turning a lever which throws in the gears for the desired speed of the drum. When this is done, the drum attains its full velocity practically instantly. Several speeds of the drum are available, but only the two highest have been used in these experiments. These two speeds are intended with the standard drum to give surface velocities of 50 cm. and 100 cm. per second. With the small drum used in the camera the velocities are, of course, reduced in proportion to the circumference and are 14 cm. and 28 cm. respectively.

With the illumination already described it was found that even at the highest speed fair contrast was obtained in the exposed film with ordinary developer. By using a concentrated developer warmed to about 28°C. excellent contrast was obtained without injury to the film.

It was found that if the metal handle by which the gears are shifted was grasped with the bare hand, oscillations were induced in the string synchronous with the revolutions of the armature in the motor. To obviate this difficulty a hard rubber handle was fitted over the regular handle and to this was fastened a brass cross bar. To the latter was soldered a copper wire by which it was connected to earth. As an additional precaution, a tin shield, also led to earth, was fitted over the whole motor. When the motor is operated by the grounded brass cross bar, no oscillations of the string are induced.

Time is recorded on the film by means of a tuning fork kept vibrating by an electro-magnet with platinum contact interrupter. One limb of the tuning fork, which makes 100 complete vibrations per second, is placed in the path of the beam of light.

For the purpose at hand this apparatus has proved quite satisfactory. Its salient feature is the facility with which large numbers of observations can be made in quick succession and with great economy of film. With a little practice it has been found possible to throw in the gears, stimulate the nerve with the other hand and throw out the gears in the space of 0.16 second, as is shown by the time-marker on the exposed film. Longer exposures can be made at will, up to the limit of the film, where longer series of events are to be recorded. No readjustment of any part of the recording apparatus is required between exposures. It is possible, therefore, with a 50-foot film, to take at the highest speed of the drum over 250 successive exposures as rapidly as is desired, or double that number at the second speed.

D. Stimulation apparatus

For stimulation a Berne inductorium[21] was used, except in the first experiment (preparation 2) from which records have been reproduced; in this experiment a Gaiffe coil was employed. The Berne coil was calibrated with Martin's apparatus in accordance with his method.[22] The primary current was supplied by an

[21] This coil was exactly like that shown in figure 9 of Martin's book. Measurement of Induction Shocks. New York, 1912, p. 30.

[22] Martin: Loc. cit., p. 55.

Edison storage cell and determined by an ammeter in the circuit. To show the instant of stimulation there was introduced into the primary circuit a small signal magnet whose recording lever is very light and when released from the magnet on the break is pulled back with great rapidity by a wire spring. A narrow strip of paper cemented to this lever was placed in the path of the beam of light before the slit in the camera. The quickness of this signal was tested by connecting it in parallel with the string galvanometer, diverting just enough current through the latter to give a good excursion. On examining the record of the break of a constant current with this method at the highest speed of the film the lag was found to be extremely small. Experiments with more recently constructed apparatus capable of determining time to about 0.1σ have shown that the first perceptible excursion of the signal magnet occurred between 0.6 and 0.7σ after the current was broken. In all time measurements the nearest black line in the film, showing where it had been at rest with the shutter open, was used as a base. Since it was necessary to lead the wires supplying the signal magnet close to the motor which operates the drum, these were enclosed in lead sheathing and the lead put to earth, to insure further against the induction of electrical disturbance, in the string.

In approximately the first half of the experiments the Martin knife-blade mercury key[23] was employed. This proved satisfactory at first, but through a defect which later appeared in the operation of the key at our disposal it was found to make a brief secondary closure of the circuit after breaking, thus giving rise to three successive shocks. Sometimes this was shown by the signal magnet, but more often the secondary closure was of too brief duration to deform the signal record, yet it was evidenced in the response of a nerve under direct stimulation which yielded two or three separate action currents instead of one.[24] On this account it was replaced by a key made on a plan recommended by Dr. H. B. Williams. This consists of a

[23] Martin: Loc. cit., p. 63.

[24] This defect was afterwards remedied by the introduction of a strip of steel to guide the knife-blade. See Martin: This journal, vol. 36, 1915, p. 237.

small glass cup containing clean redistilled mercury connected with one terminal, and a rod of copper tapered to a sharp point and amalgamated, connected with the other. This rod is dipped into the mercury and withdrawn by means of a hard rubber lever operated by hand. This key can be relied upon to give clean makes and breaks. There may be slight variations in the intensity of the break shocks dependent on the speed with which the copper point is withdrawn from the mercury; but in a control experiment with threshold stimulation of a frog's muscle the strength of the shocks was found not to vary by as much as 2 per cent when the speed of withdrawal was purposely varied as widely as it well could be in operation by hand. This means that for the degree of accuracy requisite in these experiments it was quite satisfactory.

In nearly all of the experiments the primary circuit included in series the cell, the key, the signal magnet, the primary coil, the ammeter and a small resistance coil (2, 3 or 4 ohms) to reduce the current to the desired value. The strengths of the stimuli were determined in Z units according to Martin's method.[25] In three experiments in which weak stimuli were desired the circuit was divided, the greater part of the current going through the signal magnet which would not operate on less than 0.20 amp., while only about 0.1 amp. was allowed to go through the primary coil. The provision of a shunt rendering the break less abrupt through inductance, caused the break shocks to be far less intense than would be the case on complete interruption of a current of the same strength. In consequence, it was impossible to apply the Martin method to the evaluation of these shocks, and it was quite evident from a comparison by the two methods of thresholds in the same preparation that the shunt greatly reduced the physiological intensity of the shocks.

E. Experimental procedure

Throughout this investigation decerebrate cats were used exclusively. Decerebration was performed under ether anaesthe-

[25] Martin: Measurement of Induction Shocks, p. 73.

sia in the manner described by Sherrington and one of us.[26] The essential features of the operation are the ligation of the carotids and the removal of the entire brain above the level of the posterior corpora quadrigemina.

Although etherization was stopped simultaneously with the completion of decerebration the flexion reflex was usually not obtainable for an hour or more and was seldom vigorous until two or three hours had elapsed. In order that the observations should be made after the vigor of the reflex had been fully regained, the animal was usually left undisturbed for an hour or two after decerebration before beginning the subsequent preparations which required from one and one-half to two and one-half hours. From the beginning of anaesthetization the animal was kept on an electric heating pad whereby the body temperature was kept approximately normal until just before the observations were begun. The pad was then disconnected to avoid the danger of leakage of current.

The motor nerve selected was the peroneal. The principal muscle which it innervates is the ankle flexor, tibialis anticus; it is readily dissected out over a distance of 12 cm., in which it gives off no branches, between the hip and the knee; this renders it a favorable nerve to work with. We desired if possible to record the action currents in the nerve without disturbing its continuity or paralysing the muscle. To place two electrodes on the uninjured nerve and thus record diphasic action currents while the muscle was still innervated was not found practicable for the following reasons: First, it was almost impossible to maintain contacts between electrodes and nerve which could be relied on not to shift, without making contact with other tissues, or else putting a strain on the nerve which would rapidly impair its conductivity. Furthermore, it was difficult, even with the maximum length of nerve available, to separate the electrodes far enough to enable the string to follow the phases of the action current, overlapping as they do on account of the high velocity of the nerve impulse unless several centimeters

[26] Forbes and Sherrington: This journal, vol. 35, 1914, p. 367.

intervene between the leads. Finally, it is only in case the impulses are sent down the nerve trunk 'in a volley,' i.e., simultaneously in all the fibres, that we should expect to obtain an intelligible record with the diphasic method, since otherwise the second phase in some fibres would neutralize the first phase in others and a confused record at best would be obtained. Since it is not at all certain that central discharges travel simultaneously in all the fibres of a given nerve trunk,[27] it seemed best to simplify the records by rendering the action currents monophasic.

An attempt to do this without injuring the nerve was made in the following way: One electrode was placed on the motor nerve, and the other (indifferent) electrode on a muscle (paralyzed by section of its nerve) on the other side of the leg. It was found, however, that with this arrangement, the action current of the innervated muscle following that of the nerve introduced itself into the circuit and confused the result. The method was therefore abandoned.

The method finally adopted was to cut the nerve at its entrance to the muscle and render the part in contact with the distal electrode inactive. In one experiment this was done in the classical manner by devitalizing the distal portion in hot Ringer solution. In all other experiments, however, the nerve was simply crushed with a hemostat to block the impulses at a point about midway between the leads. This method saves time, and no appreciable difference in the result could be detected, except that there is less demarcation current to compensate.

The operative procedure subsequent to decerebration was as follows: A long incision was made in the lateral aspect of the thigh, from hip to knee. The biceps femoris muscle was dissected away from the fascia along its anterior margin and its insertion divided; it was then reflected back, thus exposing the sciatic nerve and its terminal branches as far as the knee, and opening a region of easy access to the femur for the insertion of a clamp. The muscles covering the sciatic nerve in the neigh-

[27] Buytendyk: Loc. cit., p. 44.

borhood of the hip were then divided and the nerve laid bare almost to its point of emergence through the great sciatic notch. The peroneal nerve was then dissected carefully from the bifurcation of the sciatic to its entrance to the tibialis anticus muscle. It was also dissected away from the rest of the sciatic trunk as far back as the hip. With fine scissors this operation can be performed rapidly and with little or no trauma to the nerve. The popliteal nerve was then ligated near the knee and cut distal to the ligature. Platinum stimulating electrodes arranged to give ascending break shocks were then temporarily applied to the central end of the cut popliteal nerve, and the threshold for reflex contraction of the tibialis anticus was determined in Z units for break shocks. When only the activity of the motor nerve was to be studied the peroneal nerve was then crushed at a point about 3 cm. from its entrance to the muscle and cut 2 or 3 cm. distal to the crush. To the popliteal nerve was then applied a pair of Sherrington shielded electrodes for afferent stimulation. A clamp was fastened to the femur and secured in a rigid stand, thereby practically immobilizing the limb. Sometimes, further to insure immobility, the hamstring nerve was cut; sometimes it was left so that contraction in the muscles should serve as a visible index of the reflex. The stimulating electrodes were now connected with the secondary coil for ascending break shocks and the peroneal nerve led through a small opening into a moist receiving chamber where it was laid across a pair of non-polarizable "boot" electrodes about 3 cm. apart with the crush approximately midway between. This receiving chamber is a small hard rubber box clamped firmly to a stand by which it is held close to the animal's hip. The boot electrodes are fitted in notches in the wall of the chamber where they are held in place with wax. The hole through which the nerve enters the chamber was plugged with a paste of kaolin and Ringer solution which served both to conserve the moisture within the chamber and to steady the nerve and prevent any vibration imparted to it by motion of the animal from being transmitted to the electrode contacts.[28] As a further

[28] Cf. Dittler: Loc. cit., p. 583.

safeguard, the nerve was drawn into the chamber far enough to allow a little slack between the kaolin plug and the proximal electrode. Only a short length of nerve was exposed to the open air between the animal's body and the entrance to the moist chamber. In most experiments this was protected from drying by a flap of skin cut from the thigh and wrapped around it.[29] As soon as the nerve had been placed on the electrodes the circuit through the string was closed, and the demarcation current compensated by means of the cell and slide wire described above. Except when effects of fatigue were especially sought a rest of at least ten seconds was allowed between successive observations on the reflex.

In nearly all experiments, after a series of responses in the nerve had been recorded, it was severed at the hip and stimulating electrodes applied at the central end of the isolated portion, arranged for descending break shocks. A series of responses was then recorded to afford a comparison of the responses in the nerve under reflex and under direct stimulation.

EXPERIMENTAL RESULTS

A. The typical flexion reflex

The flexion reflex has been examined by the method described above in twenty-five decerebrate cats. The monophasic electrical responses obtained from the peroneal nerve in the flexion reflex induced by single break shocks applied to the popliteal nerve are, in the majority of cases, such as are shown in figures 5 and 6. In figure 6, (A) in all cases shows the reflex responses to maximal or approximately maximal break shocks, (B) shows the responses to maximal break shocks applied directly to the motor nerve, (C) shows the calibration curves obtained with

[29] In our first experiments before the moist receiving chamber was devised, we used a method for which we are indebted to Dr. H. B. Williams, which consisted merely of leading the nerve over a glass hook and then, with enough slack between to insure steady contacts, over the boot electrodes set up in the open air. This sufficed for a brief experiment, but the drying of the nerve limited the time available for satisfactory observations far more than when the moist chamber was employed.

the same tension of the string and the same (or approximately the same) resistance in circuit as was included when the nerve was under observation. This resistance in each case was de-

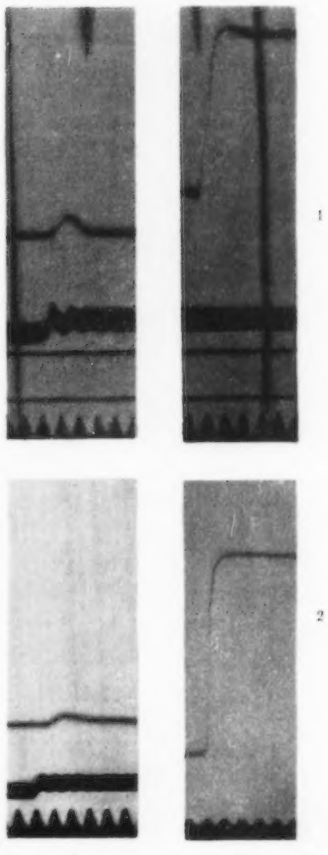


Fig. 5. *A*, typical monoplasic reflex responses of peroneal nerve to single maximal induction shocks. *B*, calibration curves, see text. *1*, string *C*; *A*, preparation 2; *B*, $\frac{20 \text{ millivolts}}{\text{string} + 74{,}000 \text{ ohms}}$. *2*, string *E*; *A*, preparation 20; *B*, $\frac{20 \text{ millivolts}}{\text{string} + 28{,}000 \text{ ohms}}$. In this and all subsequent records the top line shows the excursions of the string. The second line (where present) shows the time of stimulation. A fall in this line shows the make, a rise the break of the primary current. The small oscillations following the break are vibratory and do not indicate secondary closure of the circuit. The bottom line records time; each complete vibration = 0.01 second.

termined in the following manner. The demarcation current was compensated and then the compensating voltage was shut off from the circuit which otherwise remained unchanged. Thus was determined the excursion of the string in response to the

uncompensated demarcation current. The two-way double-throw switch (*D.S.*, fig. 1) was then thrown to the substitution resistance box (R_2) and a resistance found through which the compensating voltage produced the same excursion.

B. Reflex time

The first property of the responses to consider is the latency or reflex time. This interval between the stimulus and the response was measured on the film in over two hundred records obtained from seventeen preparations.

Fig. 6. Description in text. Strength of induction shocks in *Z* units, and values of calibration curves as follows:

1. Preparation 5. String C.
   Stimulus, A, $\frac{584}{K}$ Z; B, $\frac{39}{K}$ Z; C, $\frac{10}{\text{String} + 46{,}000}$
2. Preparation 6. String C.
   Stimulus, A, $\frac{104}{K}$ Z; B, $\frac{26}{K}$ Z; C, $\frac{10}{\text{String} + 40{,}000}$
3. Preparation 8. String D.
   Stimulus, A, 73 Z; B, 73 Z; C, $\frac{10}{\text{String} + 40{,}000}$
4. Preparation 9. String D.
   Stimulus, A, 38 Z; B, 38 Z; C, $\frac{10}{\text{String} + 37{,}000}$
5. Preparation 12. String D.
   Stimulus, A, 197 Z; B, 197 Z; C, $\frac{20}{\text{String} + 39{,}000}$
6. Preparation 13. String D.
   Stimulus, A, 59 Z; B, 6.8 Z; C, $\frac{20}{\text{String} + 20{,}000}$
7. Preparation 19. String E.
   Stimulus, A, 75 Z; B, 17 Z; C, $\frac{50}{\text{String} + 28{,}600}$

In Nos. 1 and 2, and in Fig. 11 No. 3, the *Z* units are given divided by an unknown constant *K*. This signifies the introduction of a shunt in the primary circuit which reduces the intensity of the break shocks (see p. 132). In the fractions indicating the currents used in calibration curves the numerators denote millivolts, the denominators ohms in series with the string. The tension of the string in No. 7 is higher than in any of the others. In No. 6C, the magnetic field was about half as strong as in all other records.

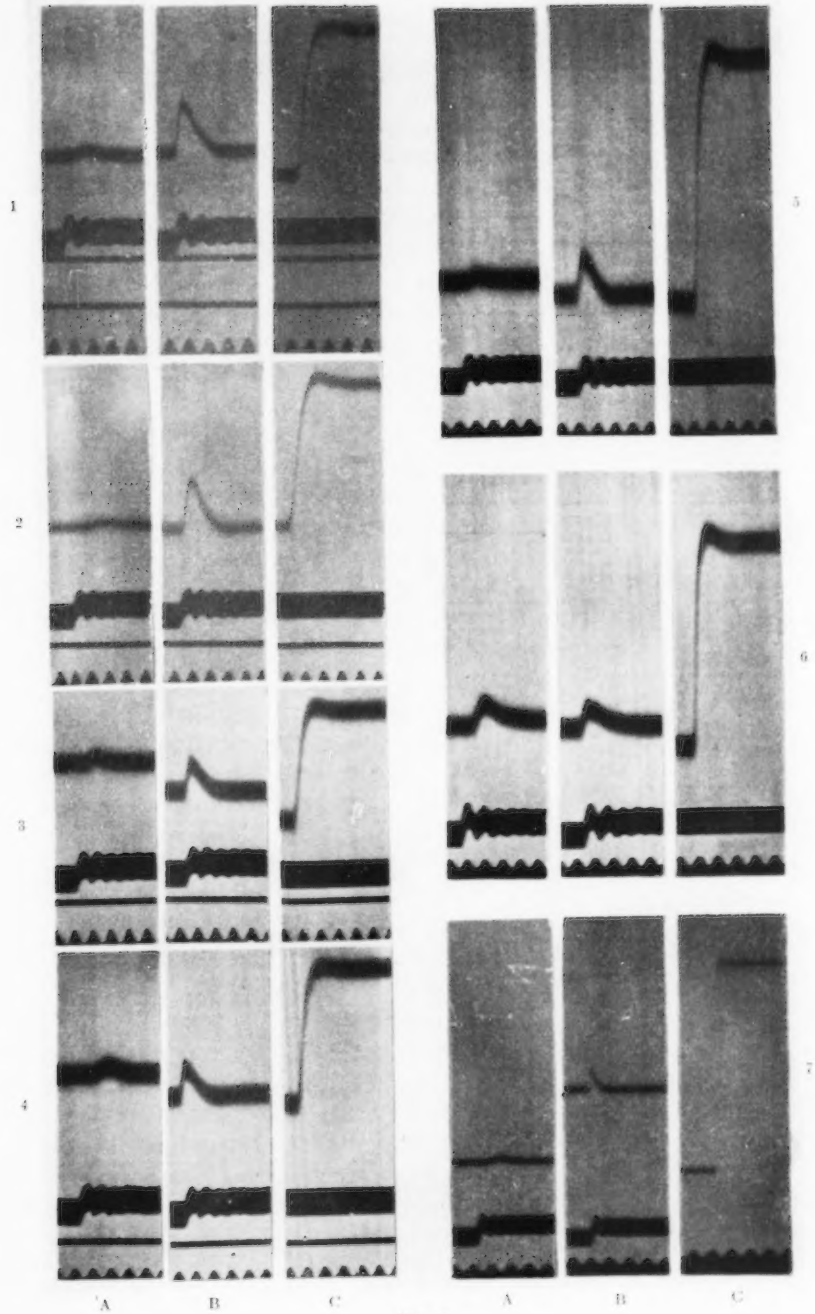


Fig. 6

As has been indicated above, time measurements can be made with an error of less than 0.5σ provided the excursion of the string has been sufficiently abrupt. In the majority of reflex responses this condition has not been realized, and the point of departure of the string from its resting position has been so ill defined that an error of nearly 1σ may exist. For example, in one record of average clarity the measurement made between the first motion of the signal magnet and the first motion of the string indicated a time interval of 9.5σ, and it could only be stated with certainty that the time lay between 8.7σ and 10.2σ.

It has been noted above that the signal magnet had a delay of about 0.6σ. Consequently, this amount was in each case added to the time as measured by comparison with the signal magnet curve. In some experiments, for reasons which will be discussed in a subsequent paper, an electrical disturbance passing through the string at the instant of stimulation was large enough to show a small notch in the record (fig. 9). Where this was clearly marked, time measurements were taken directly from it instead of from the signal magnet. Where they were taken from both in the same records, they showed an average difference agreeing fairly well with the lag of the signal magnet as measured with the more accurate apparatus. Some of the records seem to show that the delay of the signal magnet varied somewhat, but in all cases it seems to have been so near its average value, 0.6σ, as not to introduce an additional error of more than 0.3σ or 0.4σ at most.

The results of these measurements are as follows. The smallest individual measurement of reflex time was 7.7σ; the largest was 12.8σ. An average of all the measurements for each preparation was taken, and the smallest average was 8.1σ, the largest 11.6σ. A general average made up of the averages for the separate preparations was 9.6σ. One experiment was especially favorable for accurate time measurements. The arc lamp was employed for illumination and the preliminary notch in the record showing the instant of stimulation was very sharp and well defined. The latencies measured in three records from this preparation were 8.0σ and 8.3σ and 8.0σ, making an average

of 8.1σ. These measurements can be relied on to be within 0.4σ at most of the true value. The record showing a latency of 8.3σ is reproduced in figure 9.

In interpreting these results the following variables must be considered: the lengths of the afferent and efferent peripheral nerves lying in the reflex path, the body temperature and the temperature and extent of the exposed portions of the nerves. In all cases the stimulating electrodes were applied to the popliteal nerve at a point between 3 cm. and 6 cm. from the hip; in a great majority this distance lay between 4 cm. and 5 cm. In all but one experiment, the proximal leading off electrode touched the peroneal nerve between 7.5 cm. and 9.5 cm. from the hip, usually between 8 and 9 cm. A dissection of the lumbosacral plexus in an average sized cat showed that in the case of the nearest roots involved in the reflex the afferent fibres travel 8.5 cm. from the hip before entering the cord, and 9.4 cm. in the case of the farthest roots. The corresponding distances for efferent fibres are 8.5 cm. and 9.2 cm. Since we are concerned with the earliest response, it is probable that the shortest path is the one to consider. In all experiments the peripheral nerves were dissected out from the surrounding tissues from the hip to the points of stimulation and leading off. The afferent nerve after application of the shielded electrodes was covered by the ham-string muscles whose temperature probably remained somewhat below that of the rest of the body throughout the experiment. The portion of the motor nerve distal to the hip was exposed to room temperature, about 21°C. That portion of the sciatic nerve central to the hip was at body temperature. This was not recorded during the observations, but in almost all cases it was maintained between 35°C. and 38°C. until just before the commencement of the observations. Two notable exceptions were associated with exceptionally long reflex times. One of these, yielding the longest average reflex time of all (11.6σ) was accidentally allowed to cool through a defect in the heating pad. At the beginning of the observations the body temperature was found to be 32.7°C.; about an hour after the end of the experiment it was 29.3°C. The next longest average time (11.2σ)

occurred in an animal whose temperature, though not taken immediately before the experiment, may yet be inferred from earlier and subsequent observations to have been between 32°C. and 33°C. during the experiment. The shortest average time (8.1σ) occurred in an animal whose temperature remained at about 36°C. throughout. From these facts it appears that the longest times recorded are the result of cooling of the animal to an abnormal degree. An average of the remaining preparations after the exclusion of those in which excessive cooling probably rendered the delay abnormal, gives the observed reflex time as 9.1σ which is probably more nearly normal than the higher value given above. Still it is not improbable that if body temperature had been maintained strictly normal in all experiments, an average nearer 8σ than 9σ might have been obtained. An experiment has been quite recently made with the new apparatus already alluded to, with a film operating at 44 cm. per second. The proximal leading-off electrode was about 7 cm. from the hip, the body temperature between 34° and 35°C. A series of six records gave an average observed reflex time of 7.7σ. Later, when the body temperature had fallen to nearly 32°C., an average of 8.0σ was obtained. The figures are probably more accurate than those with the slower apparatus, but are also probably those of an unusually quick preparation. There is some question whether the variation in readings from individual preparations is due mostly to the error inherent in making accurate measurements of such small distances or whether there was in reality any considerable variation in the reflex time in a given preparation. We feel certain that in some cases at least the observed variation exceeded the range of observational error and showed a real variation between successive records. No correlation could be found between these variations and the strength of stimulus. This may not prove that no such correlation can exist with appropriate stimuli, for practically all our observations suitable for measurement were those in which maximal and supra-maximal stimuli were employed.

In estimating the "reduced reflex time," or time of transmission through the spinal cord, from the above figures it seems valid

to assume the velocity of impulses in those portions of the nerves which were at body temperature to be 120 metres per second.[30] The velocity in the portion of the motor nerve at room temperature probably was more nearly that commonly found in amphibian nerves at room temperatures (about 30 metres per second). The best measurements at our disposal made at room temperature with the same apparatus used in these experiments show a velocity of about 24 meters per second for impulses in the nerves which we are dealing with. These afford only a rough approximation, and the true value is probably somewhat nearer the Helmholtz figures. Assuming a velocity of 30 metres per second for this part, the time to be subtracted from the total reflex time will be between 2.5σ and 3.2σ, almost always between 2.7σ and 3.0σ.

In one instance in which the proximal lead was brought 2 cm. nearer the hip between two sets of observations no shortening of reflex time appeared to result, although the increased cooling of the animal cannot have amounted to more than about 0.6°C. in the interval. We can only guess at the rate of conduction in the short length of afferent nerve covered by the dissected muscle distal to the hip, certain only that it will lie somewhere between 30 m. and 100 m. per second. The difference between these extremes will make a difference in the subtraction amounting to about 1σ. If we assume a medium rate of 60 m. per second the error will probably be insignificant. At this rate the subtraction will be between 0.6σ and 0.9σ. The total deduction for the cooled portions must lie, then, between 3.1σ and 4.1σ; on average it will be about 3.6σ. The deduction for the portions of the nerves lying proximal to the hip should have a practically constant value of approximately 1.4σ. Making the average deduction from the average observed latency the average reduced reflex time is about 4.1σ. From the figures given above, it is safe to say that the extreme limits between which the "reduced reflex time" must normally lie are 6.5σ and 2.0σ. This allows for making the maximum subtraction from the minimum

[30] Piper: Pflüger's Archiv., vol. 127, 1909, p. 474. See also Jolly: Loc. cit. and Hoffmann: Loc. cit.

observed time and vice versa, and the latitude is probably excessive. We think it safe to conclude that in the flexion reflex in the cat at normal temperature the "reduced reflex time" lies, in general, between 3σ and 5σ. The recent experiment with the high speed film furnished more definite data than most of the others, and in this the reduced reflex time is estimated at about 3.4σ, certainly between 3.0σ and 3.8σ. The results of these measurements are in strikingly close agreement with those obtained by Jolly[31] who deduced as the "synapse" time of the flexion reflex in the spinal cat 4.3σ. The values are considerably smaller than that which Hoffmann[32] deduces from his experiments on the tendon reflex in man or that which Buchanan[33] and Wundt[34] have found in the frog. However, the diversity in size between the spinal cords of the cat and of man may well account for the former difference, and the diversity in temperature for the difference found between the cat and frog. It is important also to note that Hoffmann was dealing with a tendon reflex (proprioceptive) in extensor muscles, while we are dealing with a different type of reflex involving only flexor muscles.

C. Other properties of the reflex response

Comparison of the typical reflex response with that of the same nerve to direct stimulation (fig. 6, columns A and B) reveals two other striking differences besides the latencies. First, the magnitude of disturbance is in all cases much smaller with maximal reflex stimulation than with maximal direct stimulation. Secondly, the disturbance when it appears is far less abrupt in its onset in the reflex than in direct stimulation; that is, it requires more time to reach its greatest magnitude. No. 6 in figure 6 does not contradict the first proposition as it might appear to. The direct stimulus in this case was considerably below maximal value, the reason being that in this experiment the

[31] Jolly: Loc. cit.

[32] Hoffmann: Loc. cit. Cf. also Sherrington: Integrative Action of the Nervous System, p. 19.

[33] Buchanan: Quart. Journ. Exp. Physiol., vol. 1, 1908, p. 1.

[34] See Starling: Human Physiology, 1913, p. 342.

defect in the circuit breaking key already referred to was at its worst and the observation shown at B was the only one obtained from this nerve in which a single impulse was recorded. However, the fact that these two excursions are the same height makes the contrast between the time relations all the more evident.

The extent of this difference in the rapidity of development of the electrical disturbance is difficult to determine exactly. No attempt has been made to apply to the curves the mathematical analysis expounded by Einthoven, but a glance at the calibration curves will show that the string cannot follow accurately the potential changes in the nerve impulse under direct stimulation. Figure 7 shows three records of maximal impulses in the same nerve stimulated directly, within a few minutes of each other at three different tensions of the string. In A the tension was such that 1 cm. excursion = 62×10^{-8} ampere, in B the string was twice as slack as in A, i.e., 1 cm. = 31×10^{-8} ampere); in C it was ten times as slack as in A (1 cm. = 6.2×10^{-8} ampere); in B the string was at about the limit of periodicity as appears from the corresponding calibration curve. At the highest tension (A) in this series the full excursion in the calibration curve is reached in 2.2σ; in B the full excursion is reached in 5.3σ; while in C it is only reached in about 30σ. In the corresponding records of action currents the durations of the ascending limbs of the curves are approximately 1.3σ, 1.9σ and 4.7σ respectively. Thus even at the highest tension the string has not had time to reach its full excursion before the maximum of the action current is over. The time of maximum potential difference probably occurs at approximately the steepest point in the curve, i.e., less than 1σ, possibly only 0.5σ, after the beginning of the disturbance.[35]

In the case of the reflex response the string must far more nearly follow the electrical disturbance relatively than in the case of direct stimulation. But even here the lag is probably such as to render appreciable the difference between the curve

[35] Cf. Erlanger and Garrey: This journal, vol. 35, 1914, p. 398, footnote. See also Gotch: Journal of Physiology, vol. 28, 1902, p. 405.

traced by the string and a true curve of potential difference plotted against time. Yet the rise in the curve from the base line is so gradual that we may safely assume that its distortion by the lag of the string is insignificant in the case of the reflex

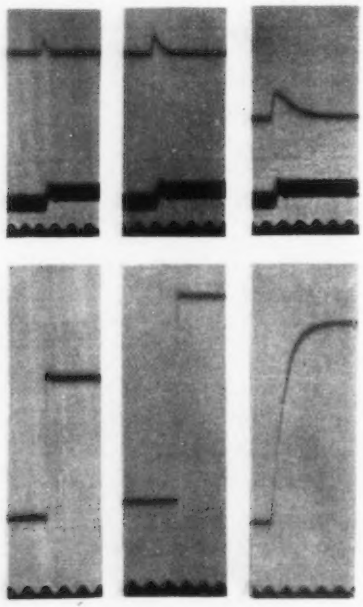


Fig. 7. Description in text. Preparation 19. String E.

A, Stimulus, 75 Z; Calibration $\frac{80}{\text{String} + 46{,}000}$

B, Stimulus, 75 Z; Calibration $\frac{50}{\text{String} + 28{,}000}$

C, Stimulus, 75 Z; Calibration $\frac{10}{\text{String} + 28{,}000}$

compared with that in the case of direct stimulation. Since the lag of the string enters equally into the records of both events but proportionally retards the phases of the direct response far more than those of the reflex response, it follows that the real difference in the abruptness of development of the

electrical disturbance is even greater than appears in the records. Considerable variation appears in the shape of the reflex records as obtained from different preparations; in general, the rise from base line to maximum occupies a time varying from 4σ to 9σ, the lower figure being obtained only with a fairly tight string. From a study of the calibration curves and records of direct stimulation at various tensions of the string, it may be inferred that the above figures indicate a time varying roughly from 3σ to 6σ occupied by the reflex electrical disturbance in its increase from zero to its maximum. It may be noted that the time occupied in the subsidence of the process is, as nearly as can be judged, about the same in both the reflex and the direct response.

In general, it may be said that as compared with the direct response, the reflex action current appears after a latency of about 9σ, then rises to a maximum which is reached from four to ten times as long after its onset as is the case in the impulsed directly evoked from the nerve by a single shock; and the maximum when reached is much smaller even in a maximal reflex than is evoked by maximal stimulation of the nerve.

In connection with the magnitude of disturbance the observation of Camis[36] is important. He reported that maximal stimulation of either the peroneal or popliteal nerve alone failed to evoke as much reflex contraction of the flexor muscles as maximal stimulation of both together. In other words, neither of these nerve trunks was able alone to evoke the maximum response of which the reflex centre was capable. In view of this, we should not expect to find the response in the motor nerve in the reflex as great as when all its fibres are excited electrically. Furthermore, it must be remembered that nearly half of the fibres in the peroneal nerve are afferent and play no part in the motor discharge from the centre, and yet these fibres undoubtedly contribute a full share in the response to direct stimulation. There is some doubt whether even these two considerations taken together can explain alone the great difference in magnitude between the reflex and the direct response, considering the

[36] Camis: Journal of Physiology, vol. 39, 1909, p. 228.

vigor of the reflex contraction which can be evoked by a single shock. Perhaps we shall have to seek further yet to account fully for the difference. The discrepancy in the time relations may furnish some clew.

For the strikingly more gradual development of the reflex response than of the direct, two conceivable explanations present themselves.

(1) It might be inferred that impulses arising in a reflex centre are different in kind from those evoked by an artificial stimulus directly applied to the nerve trunk. In one case the nerve fibres receive the impulses from a natural source, in the other case from a wholly unnatural source and in a manner different from any occurrence in the course of their normal functioning. Conceivably, the individual impulses arising in the neurones from reflex excitation are qualitatively different from those artificially induced and rise to their full intensity more gradually. Such a view is quite at variance with the conception of the nerve impulse which has developed from the researches of Lucas, Hill and Adrian.[37] Their results make the propagated disturbance in nerve appear to be a sort of explosive event whose character is always the same by whatever agent evoked, so long as the condition of the nerve remains unchanged. It further appears, so far as individual fibres are concerned, to obey the "all-or-none" law; that is, its magnitude is always the same in normal fibres regardless of the strength of the stimulus. On the other hand, it is to be remembered that all these researches on the properties of the nerve impulse have been carried out with artificial stimuli, and it is still conceivable that the reflex centre can induce in nerve fibres a different kind of activity which we have found no means of duplicating.

(2) The more gradual rise of the electrical disturbance in the case of the reflex may be quite as easily explained in a way which

[37] Lucas: Journal of Physiology, vol. 39, 1909, p. 331; ibid., vol. 40, 1910, p. 225; ibid., vol. 41, 1910, p. 368; ibid., vol. 43, 1911, p. 46; Proc. Roy. Soc., vol. 85B, 1912, p. 495. Hill: Journal of Physiology, vol. 40, 1910, p. 190. Adrian: Journal of Physiology, vol. 45, 1912, p. 389; ibid., vol. 47, 1914, p. 460; ibid., vol. 48, 1914, p. 453.

harmonizes perfectly with the view that the impulse is essentially the same however evoked. It has already been suggested that we have no grounds for the conclusion that in the flexion reflex the impulses in the many neurones making up the motor nerve are discharged "in a volley" rather than in "platoon fire," to use Brucke's phrase.[38] They might conceivably start down the nerve trunk simultaneously in all the fibres. Yet it is quite as likely, if not even probable, that the reflex times in the hundreds of separate arcs will not be exactly the same, and that the arrival of the various outgoing impulses at a given point in the nerve will be spread out over a considerable period of time. Just such a scattering in time would perfectly explain the more gradual development of the observed electrical disturbance at the point where it is recorded. It would also contribute another factor to account for the greatly reduced intensity of disturbance as compared with the direct response; for if at any given instant only a small percentage of all the fibres taking part in the reflex are at the height of their activity, at no time will there be so great a disturbance as if all were active at once. This consideration taken in connection with those already mentioned, namely, the fact that nearly half the fibres involved in the direct response are afferent and the fact that by no means all of the motor fibres are called into action by stimulation of a single afferent nerve, may well account for the smallness of the action current obtainable from the maximal reflex.

D. The diphasic response

It was hoped that by recording the reflex response with diphasic leads (i.e., with both electrodes on the uninjured nerve trunk) some light might be thrown on the question just raised, namely, whether the reflex discharge is a "volley" of impulses which individually are different in kind from those induced by direct stimulation, having a more gradual onset, or whether it is a "platoon fire" or over-lapping series of impulses individually identical with those evoked by direct stimulation. To this end

[38] Brucke: Sitzungsberichte der Weiner Akad., 1877. See Buytendyk: Loc. cit.

a few experiments were performed with the following change of method from that described above. A pair of shielded platinum electrodes in a glass tube on the Sherrington pattern was fastened at the entrance to the moist receiving chamber so that they made contact with the peroneal nerve close to the hip and about 3 cm. central to the proximal leading-off electrode. The nerve was carefully dissected out with all possible avoidance of trauma and laid uninjured across the boot electrodes in the chamber to render the records diphasic instead of monophasic. The secondary coil of the inductorium was wired to a switch whereby it could be connected either with the usual stimulating electrodes on the afferent nerve or with the additional pair on the motor nerve. In this way reflex and direct responses could be compared in alternation, and it could be determined whether the nerve was giving true diphasic responses under direct stimulation, an important control for the experiment at hand. After recording a series of direct and reflex responses in alternation the nerve was crushed between the leads to render the responses monophasic, and a second similar series of responses was recorded. If the nerve was long enough to permit, it was then drawn along over the electrodes till the crushed point was far enough beyond the distal lead to render the responses again diphasic. A second diphasic series was then recorded and, after crushing again, a second monophasic series.

A complicating feature of this procedure is the fact that in applying a stimulus to the motor nerve impulses are sent in two directions and a flexion reflex ensues in response to those which travel centrally in the afferent fibres of the nerve. This is revealed in a secondary action current in the record following that evoked by direct stimulation of the nerve. To show what part this reflex response played in deforming the record of the initial action current we have concluded each of these experiments by severing the peroneal nerve at the hip and then recording the response to direct stimulation uncomplicated by any reflex. Usually it was found that with a fairly tight string the record of the direct impulse was nearly complete before the reflex disturbance appeared; at any rate, the latter appeared too late

in the record to confuse the interpretation. Records showing the results of such a series are given in figure 8. They show the events in the following order: (A) the diphasic reflex, (B) the diphasic direct response, (C) the monophasic reflex, (D) the monophasic direct response, (E) the same as (D) after cutting the nerve at the hip to eliminate the secondary reflex effect. This latter shows plainly in both (B) and (D) following the direct response after an appropriate latency.

When the attempt was made to see what light the comparison between the diphasic and the monophasic reflex responses might throw on the question which this comparison was intended to answer, it was found that the result was indeterminate. This

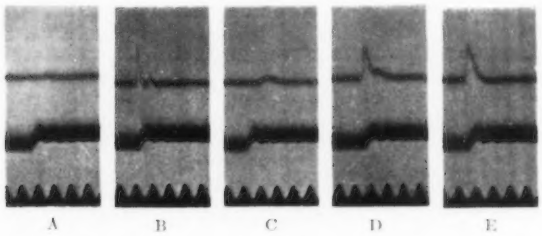


Fig. 8. Description in text. Preparation 25.
Stimulus, A, 235 Z; B, 25 Z; C, 235 Z; D, 25 Z; E, 25 Z.
String E; Tension, 1 cm. = 15×10^{-8} Amp.

was found in the following way. Hypothetical curves were plotted on coördinate paper to see what type of curve we should expect to find in each case, i.e., if we were dealing, on the one hand, with a volley of slowly developing individual impulses, or, on the other hand, with an over-lapping series of rapidly developing individual impulses. First, a single monophasic curve was drawn as a basis. This curve was not taken exactly from any known measurements, but it was given the general form known to represent roughly the rise and fall of electrical disturbance at a given point on a nerve plotted against time. For convenience the maximum was made to come 1σ after the onset, a time not far from correct. Next, by subtraction of ordinates a diphasic

curve was made such as would result if the disturbance represented by curve 1 passed at a rate of 60 metres per second over a pair of electrodes set 3 cm. apart on the nerve, this being about the distance between the leads in most of our experiments. Next, a curve was drawn to represent, as nearly as we could estimate, the observed course of the changes in potential difference as found in the typical monophasic reflex response, the maximum being reached 3σ after the onset. Then, to show the sort of response we should expect from the diphasic lead in the case of a volley of impulses individually timed like the general response, a diphasic curve was plotted by exactly the same method of subtracting ordinates by which the direct diphasic curve was derived from curve 1, but using as a basis the reflex monophasic curve. In this it was again assumed that the impulses travelled at the rate of 60 metres per second over leads 3 cm. apart. This curve will be designated the "volley reflex diphasic curve."

Next, the effect to be expected of a "platoon fire" or overlapping series of impulses was examined. A series of six monophasic curves, each similar to curve 1,[39] was plotted, and each was made to begin 0.5σ after the preceding curve. The summed or resultant curve provided a fair counterpart of a series of impulses evenly distributed over a time interval of 2.5σ. The general contour of this curve was practically identical with the curve empirically drawn to represent the apparent potential changes in the monophasic reflex response, and its maximum was reached at the same time, 3σ after the onset. Finally, a curve was plotted on the same principle to show the presumable counterpart of a "platoon fire" or overlapping series of diphasic individual impulses. Here again six component curves, each beginning 0.5σ after the preceding, were combined, but this time each was a diphasic curve timed like a direct diphasic response. The resultant curve was found to be almost indentical with the "volley reflex diphasic curve." The differences between them were so slight that it would be clearly impossible

[39] The ordinates of these were reduced throughout to one-quarter of their values in curve 1.

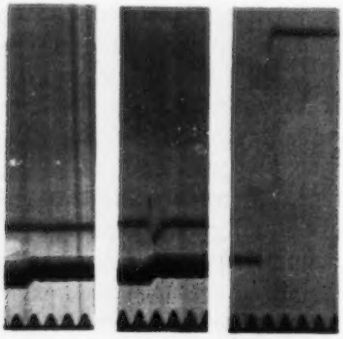
to infer from the diphasic reflex records whether they represented electrical changes of one type or the other. A similar series of curves in which a velocity of 30 metres per second throughout was assumed yielded essentially the same result. In short, unless we assume the rate of propagation of impulses along the nerve to be slower in the reflex response than in the direct, which is a most improbable assumption, we should expect to find no material difference in the diphasic records whether the slower development of the monophasic disturbance in the reflex resulted from slower development of the disturbance in individual impulses, or from the scattering in time of impulses which are individually as abrupt as those evoked by direct stimulation. The records of diphasic and monophasic responses from the same preparation, although they fail to settle the point at issue, are reproduced in figure 8 for whatever interest there may be in them.

Fortunately the answer to the question raised was accidently found in an experiment in which the animal investigated failed to yield typical reflex responses with the galvanometer. The excursions were abnormally slight and brief. It is probable that only a small proportion of the usual number of motor nerve fibres were involved in the response. The reflex records obtained by the diphasic method (i.e., before the nerve was crushed between the leads) showed clearly marked disphasic responses whose time relations were almost identical with those of the control records of diphasic responses from the same nerve stimulated directly. One of these diphasic reflex responses is shown compared with a control record and a calibration curve in figure 9. The monophasic responses obtained later from the same nerve were also exceptionally small and brief. In the diphasic reflex it may be seen (and it was confirmed by measurements on the film) that the times from the beginning of the first phase to the beginning and summit of the second phase are little if any longer than in the direct response. It appears from this that when few enough fibres respond to reflex stimulation the gradual onset of the electrical disturbance, usually so characteristic of the reflex, disappears. From this it may be fairly concluded that the individual impulses in the nerve fibres have the same time

relations in reflex action as under direct stimulation; that is, the electrical disturbance rises to its maximum in each fibre just as abruptly whether the impulses arise in the centre or from direct stimulation. In short, there is no valid reason for assuming any qualitative difference between impulses arising from natural and from artificial sources.

E. Dicrotic reflexes

The monophasic records of reflex responses shown in the figures already referred to have all at least had this in common, that only



A B C

Fig. 9. Description in text. Preparation 23. String E. Stimulus, A, 164 Z; B, 41 Z; C, $\frac{50}{\text{String} + 50{,}000}$

a single excursion of the string occurred in each response. This was not always the case. In a few preparations the response with the usual monophasic leads showed two fairly distinct summits. Records from two of these preparations are shown in figure 10. Such records do not necessarily show, what might at first be inferred, that any neurones involved in the reflex respond twice. It is quite possible and perhaps more probable that this apparent doubling of the response is merely an exaggerated case of the scattering in time of the discharge in the many neurones that make up the nerve trunk. It seems quite likely that in these cases the many hundred individual reflex arcs have

transmission times not evenly grouped about a mean, but falling distinctly in two groups. Thus, the first summit would indicate that the majority of the quickest arcs were responding, and the second summit would correspond with the reflex time of a second

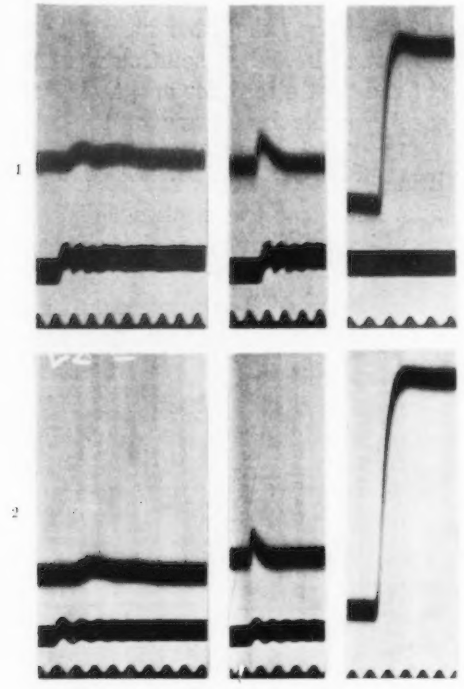


Fig. 10. String D. No. 1, Preparation 11.

Stimulus, A, 94 Z; B, 94 Z; C, $\frac{10}{\text{String} + 30{,}000}$

No. 2, Preparation 18.

Stimulus, A, 59 Z; B, 95 Z; C, $\frac{10}{\text{String} + 22{,}000}$

set of arcs. Of course the possibility that some of the neurones discharge twice is not excluded, but the other explanation seems to us the more likely.

F. The muscular response

To compare the reflex response in the flexor muscle with that of its motor nerve the following method was used. After dissecting the peroneal nerve the tibialis anticus muscle was exposed and two sutures passed through its substance; one close to the entrance of the nerve, the other near the tendinous end. Two bits of twine soaked in Ringer solution were tied round the porous portions of the boot electrodes and their ends tied firmly in contact with the muscle by means of the sutures. These were arranged to localize sharply the points of contact and to minimize the shifting of the contacts when the muscle contracted. It is believed, therefore, that the electrical disturbance due to such shift as may have occurred is insignificant. When a series of responses from the contracting muscle under reflex stimulation had been recorded, the nerve was crushed and cut as already described, and another series of responses recorded from the nerve.

In three experiments the motor nerve was cut far enough from its entrance to the muscle to permit electrodes to be applied for stimulating the muscle directly through its motor nerve. Then, while the leading-off electrodes were still in place on the muscle, records were obtained of the action current when it was stimulated in this way for comparison with its reflex response. After this was done, leading-off electrodes were applied as usual to

Fig. 11. Comparison of reflex responses from tibialis anticus muscle (A) and peroneal nerve (B). String D used in all.

No. 1. Preparation 12.

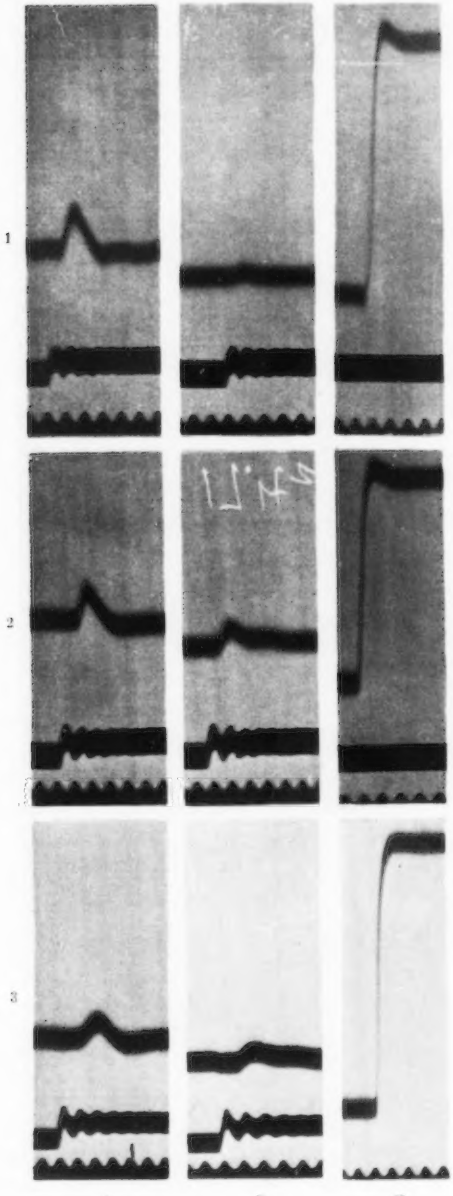
Stimulus, A, 26.5 Z; B, 144 Z; C, $\frac{20}{\text{String} + 34{,}000}$

No. 2. Preparation 13.

Stimulus, A, 19.6 Z; B, 17.4 Z; C, $\frac{20}{\text{String} + 20{,}000}$ with about half the magnetic field used in the experiments. The curve is the same as Fig. 6, No. 6C.

No. 3. Preparation 18.

Stimulus, A, $\frac{272}{\text{K}}$ Z; B, $\frac{272}{\text{K}}$ Z. C, $\frac{10}{\text{String} + 19{,}000}$


1
2
3
A
B
C

the nerve and its reflex response recorded for comparison with that of the muscle.

The method used for leading off from the muscle, i.e., exposing it in order to bring the electrodes directly in contact with the muscle substance, is not wholly free from objections. It undoubtedly has the advantage of localizing the points where activity is studied, and of leading more of the action current through the galvanometer than is possible if electrodes are applied to the intact skin over the muscle. On the other hand, exposure to the air certainly causes rapid impairment of the physiological state of the muscle. This impairment seemed to be more marked in the late autumn when the air in the laboratory was dried with steam heat than in the late spring when the air was comparatively moist and warm. In one experiment (No. 26) a combination of the method described above and that of Buytendyk was employed. Instead of exposing the whole muscle two small openings were made in the skin over the desired points and at these points strips of cloth, tied around the porous parts of the boot electrodes, were also tied to the surface of the muscle by sutures passed through its substance. Especial care was taken to avoid exposure of the motor nerve at its point of entrance to the muscle. This procedure was clearly justified by the results for the responses to both reflex and direct stimulation were notably larger than those obtained in previous experiments under otherwise identical conditions (cf. figs. 12 and 13).

The electrical responses of the muscle under reflex stimulation were found to vary far more than those of the nerve. Figure 11 shows reflex muscle responses (A) from three preparations compared with reflex monophasic responses from the motor nerves (B) recorded shortly afterwards. Figure 12 shows, in addition, responses from both muscle and nerve under direct stimulation (i.e., stimulation through the motor nerve in the case of muscle). The calibration curves in both figures refer to the response of the muscle and not of the nerve, i.e., the substituted resistance was that of the circuit including the muscle. The difference is not of great moment, for though the muscle always had less resistance than the nerve, the difference was not enough

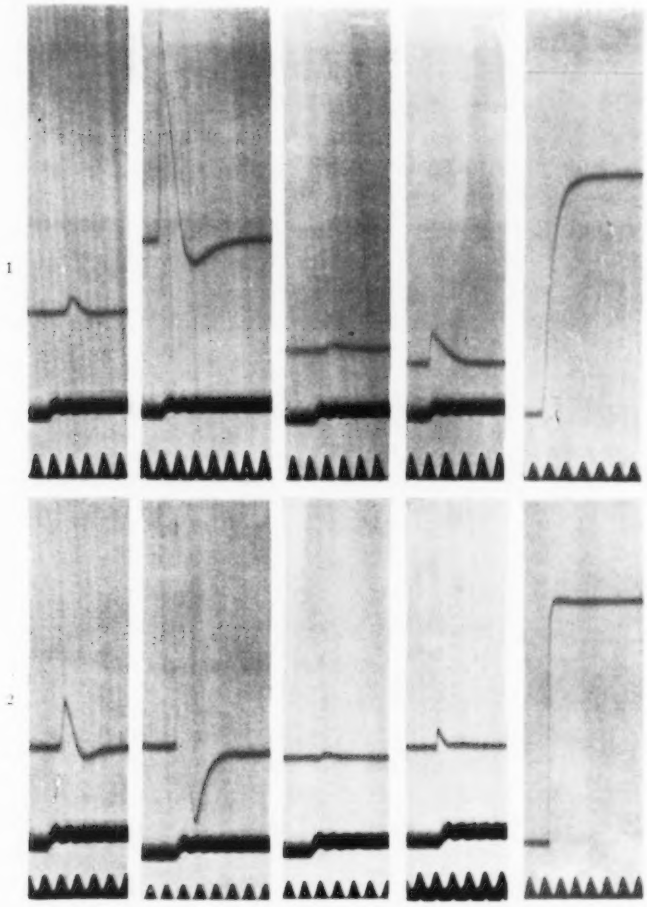


Fig. 12. *A*, reflex muscle response; *B*, response of muscle to stimulus applied to motor nerve; *C*, reflex nerve response; *D*, response of nerve to direct stimulation; *E*, calibration curve for muscle responses. All stimuli maximal. String *E* in both series. No. 1 Preparation 22. Whole muscle exposed.

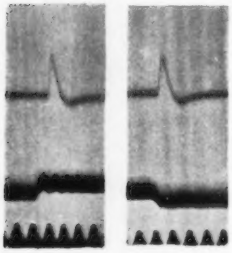
Stimulus, A, 158 Z; B, 18 Z; C, 93 Z; D, 79 Z; C, $\frac{10}{\text{String} + 25{,}000}$

No. 2. Preparation 26. Muscle exposed only under electrodes.

Stimulus, A, 93 Z; B, 41 Z; C, 334 Z; D, 25 Z. C, $\frac{25}{\text{String} + 15{,}000}$

to alter the shape of the calibration curve to any great extent. The three muscular responses shown in figure 11 appears to indicate simple twitches. In this they resemble the records shown by Jolly in figure 5 of his paper.[40] His records were obtained by essentially the same method, except that he stimulated by sudden pricking of the skin on the foot, and led off through the intact skin over the muscle.[41]

Although the majority of the reflex responses we haverecorded from muscle seem to have the character of a simple twitch, and in particular figures 12 and 13 show a reflex response whose time relations (excepting the latency) are nearly the same as the direct response, still this simple character is by no means universal.



A B

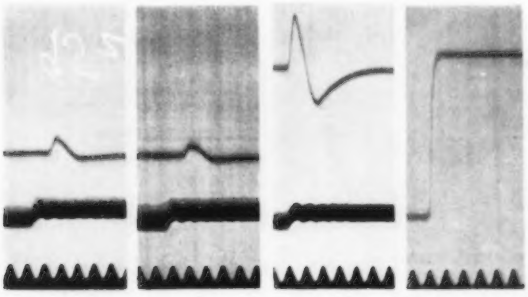
Fig. 13. Preparation 26. Response of muscle to maximal reflex stimulus (*A*) compared with response of same muscle to submaximal stimulus applied to motor nerve (*B*). Stimulus; *A*, 93 *Z*; *B*, make shock at same coil distance as in fig. 12, 2B, where break shock = 41 *Z*. For calibration curve see fig. 12, 2E. String E.

Considerable variety in the shapes of the curves are often found. In this respect the muscular responses differ strikingly from those of the nerve, for although considerable differences may be found in the records obtained from the nerves of different preparations, yet in a single preparation the responses almost invariably present the same character throughout the entire course of the experiment, often over an hour; what changes develop are almost always confined to magnitude and do not concern the time relations. That is, the responses may become larger or smaller but the curves still have the same general shape irrespective of the strength of stimulus. In the response from the

[40] Jolly: Loc. cit.

[41] In comparing the records it should be remembered that while his magnification was precisely the same as ours the speed of his plate was much greater, and his curves differ in shape from ours accordingly.

muscle, however, marked difference may be found between two successive records taken within a few seconds of each other. Figure 14 shows two records, A and P, taken within half a minute of each other from a single preparation under identical conditions and with the same strength of stimulus: the difference between them is fairly marked. Figure 15 shows a series of five muscular responses from a single preparation (the same as that which furnished fig. 12, row 2) all taken within eleven minutes and without change of experimental conditions other than in the strength of stimulus. Within five minutes of the last of these the record



A B C D

Fig. 14. Responses of muscle. Preparation 25. *A* and *B*, stimulus, 95 Z, reflex. *C*, stimulus, 25 Z, applied to motor nerve.

D. $\frac{25}{\text{String} + 30{,}000}$ String *E*.

shown in figure 12, 2A, was obtained still under the same conditions. Here, then, is a series of six records of muscular response in the flexion reflex under identical conditions and with stimuli all presumably maximal or nearly so, yet no two of them show the same shape of curve.

These observations have a bearing on the question which has been discussed by Buchanan, Piper, Garten and Dittler, whether a muscle records faithfully the impulses it receives from its motor nerve as discharged from the centre, or whether it may, under certain conditions, respond with a rhythm of its own. Of course it is not safe to base final conclusions as to what happens in pro-

longed tetanus from observations on so brief an event as the flexion reflex, and yet these observations may be suggestive in this connection.

The interpretation of dicrotic reflex responses from the muscle presents the same problem as the dicrotic response occasionally occurring in nerve. It may be that a second propagated disturbance passes over some of the fibres after they have responded once. Or it may be that the latencies of a considerable proportion of the fibres are so much longer than that of the majority that their response is marked by a distinct notch in the curve. This latter view is difficult to reconcile with the fact that of two successive reflex muscular responses to identical stimuli one may

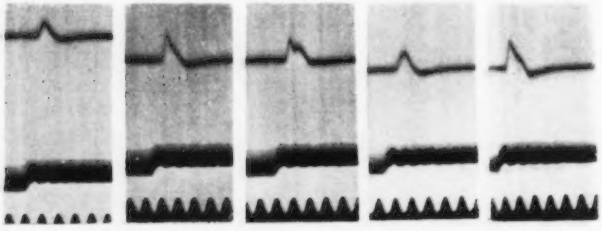


Fig. 15. Reflex responses of muscle. Preparation 26. Stimulus: *A*, 41 *Z*; *B*, 93 *Z*; *C*, 120 *Z*; *D*, 59 *Z*; *E*, 164 *Z*. For calibration curve see fig. 12, 2E.

be single and the other double. It is hard to see how the time required to evoke a reflex response in a certain group of muscle fibres could change appreciably in a few seconds without change of experimental conditions. Unless such a change of latency occurs, the only apparent explanation of the observation is that when the curve is dicrotic some of the fibres have responded twice. If this is the case our evidence supports the view that contracting muscle fibres may develop an intrinsic rhythm of response independent of the rhythm of the nerve impulses by which they are excited. It should be noted that we have not excluded with absolute certainty the possibility that the break in the primary current was not perfectly clean, and, consequently, that there may have been three shocks instead of one. That this could

be the case without deformation of the signal magnet curve was clearly shown when the defect already alluded to in the knife-blade key gave rise to double impulses in a nerve under direct stimulation. On the other hand, all the records shown in figures 14 and 15, and several others showing dicrotic responses, were obtained with the other key (in which a sharp amalgamated copper point was withdrawn from mercury), and this key never evoked anything but single impulses from nerves directly stimulated, although several hundred such records were made with it.[42] It should also be noted that the reflex response subsequently recorded in the nerve, shown in figure 12, 2C, is apparently single, although its smallness suggests that part of the nerve may have become irresponsive. In view of these facts, it seems to us fair to assume that the break shocks were single and to conclude that either some individual reflex arcs, including the muscle fibres have latencies which vary strikingly from minute to minute, or that some if not all of the fibres in the muscle under observation may respond twice in the flexion reflex as evoked by a single shock applied to the motor nerve, although apparently only a single impulse has travelled down each motor nerve fibre. In either case, the fact that a dicrotic record is obtained from the muscle when its motor nerve is yielding single excursions of the string shows that the muscle response may be deceptive as regards rhythm of innervation.

G. Summation in the muscular response

One peculiarity of the reflex muscular response, which was not apparent in that of the motor nerve, was its great intensification under the effect of rapid summation. This was brought out by the defective breaking of the primary current already mentioned. Figure 16 shows six reflex muscular responses from two preparations, all but No. 2A obtained with the knife-blade key at a time when its operation was found to be defective in a majority of

[42] Exceptions to this statement in the case of extremely powerful shocks will be discussed in a second paper. They have no bearing on the present argument.

makes and breaks. The lower row is from the same preparation (No. 13) that furnished the records in the second row of figure 11, and the first (A) of that series is reproduced again in figure 16, 2A. The latter, being a response to stimulation with the copper point key, shows the effect of a single stimulus. The first record in the upper row of figure 16 also shows a response to a stimulus which, though produced by the knife-blade key, was probably single, judging by the size and shape of the curve. Each of the four other records in figure 16 is almost certainly the response to a rapid succession of stimuli. In the upper row the third response is shown to be so by the signal magnet, while in the second, although the signal magnet shows only a simple make in the primary circuit, the stimulus was probably not simple. This probability is based on two considerations. One is the small preliminary excursion shown by the convexity upward preceding the main excursion in this record and in several other make shock records from this preparation, but not found in those evoked by break shocks; the other is the fact reported by Erlanger and Garrey[43] that even where the make of the primary current is clean the motion of the lagging armature of a signal magnet may modify appreciably the induced current in the secondary coil. Our signal magnet, though responding with great rapidity on the break, lags considerably on the make. We have, then, definite reason to infer that two of the four records in figure 16 showing exaggerated responses are the result of compound stimulation, and it is extremely probable that the other two owe their magnitude to the same cause, shocks coming in rapid succession instead of singly.

It is well established that summation plays a notable part in reflexes in general. Sherrington[44] has emphasized this, and Adrian and Lucas[45] have discussed it in an important paper in which they point out that in reflexes we are dealing with a "summation of propagated disturbances" which must be clearly distinguished from "summation of inadequate stimuli." The

[43] Erlanger and Garrey: Loc. cit., p. 388.
[44] Sherrington: Integrative Action of the Nervous System, 1906, p. 36.
[45] Adrian and Lucas: Journal of Physiology, vol. 44, 1912, p. 68.

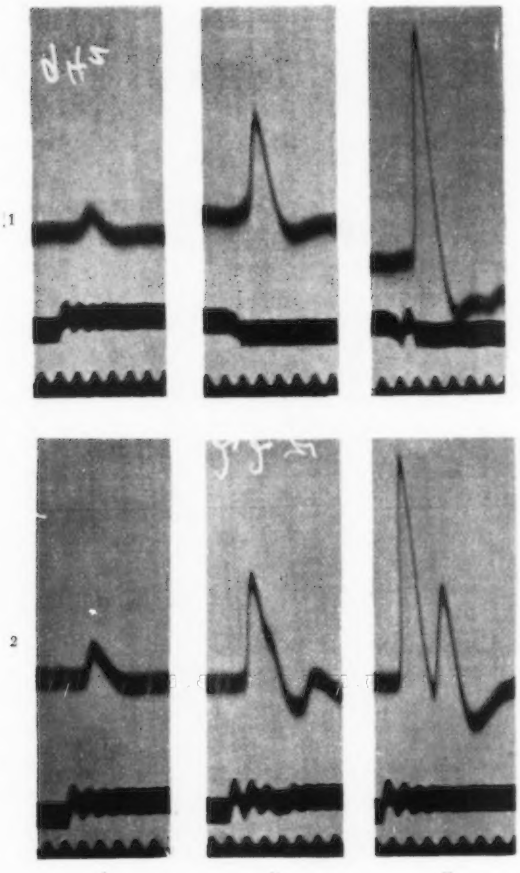


Fig. 16. Description in text. String *D*.

No. 1. Preparation 11. Stimulus; *A*, 94 *Z*. *B* and *C*, coil distances such that simple break shocks = 526 *Z* and 260 *Z*.

No. 2. Preparation 12. Stimulus; *A*, 19.6 *Z*. *B* and *C*, coil distance to give break shocks = 22 *Z*.

magnification of the reflex response under the influence of summation is in the case of the muscle very striking. In the responses from the nerve no such pronounced intensification has been recorded. Unfortunately, we have had no way of knowing positively whether the make or break in a given record was absolutely clean or not except in those cases in which the secondary closure was long enough to reveal itself in the signal magnet record. However, a long series of reflex nerve responses was recorded from each of the two preparations furnishing the records in figure 16, and almost all of these conformed very closely to the type which in each case seemed to be characteristic of a

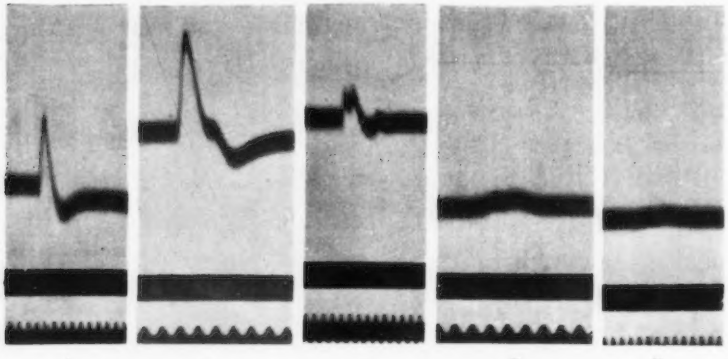


Fig. 17. Acoustic flexion reflexes recorded from muscle (*A*, *B*, *C*) and motor nerve (*D*, *E*). Preparation 12. String *D*. tension, 1 cm. 12.7 $\times$ 10^{-7} amp. For calibration curve see fig. 11, 2C. Stimulus, whistle; pitch higher in *A* and *B* than in *C*.

N.B. *A*, *C* and *E* were taken at half the usual speed of film.

single stimulus (see No. 6A in fig. 6 and No. 1A in fig. 10). It is eminently probable that the imperfection in the action of the key which appeared in a large proportion of makes and breaks both in the muscle series before, and in the series of direct nerve stimuli after, was also present in many cases in the long series of reflex nerve responses recorded between the two from both preparations. In one or two reflex nerve responses appreciable but slight intensification appears, but on the whole they show a

surprising uniformity as compared with those derived from the muscle under presumably similar conditions of stimulation. This comparison, although lacking a wholly adequate control, serves to emphasize further the lack of exact correspondence already noted between the responses of the flexor muscle and of its motor nerve under reflex stimulation.

H. Acoustic flexion reflex

In a recent paper[16] acoustic reflexes in the decerebrate preparation have been reported. In Experiment VIII of that series hip flexion was found to follow acoustic stimuli. This is unusual, the response being more commonly confined to the muscles of the pinna, neck and tail. In preparation No. 13 of our series (not reported in the paper on acoustic reflexes) the same response occurred to a more marked degree. A shrill whistle evoked a sharp twitch in the trunk and limb muscles in which limb flexion appeared dominant. As this preparation was being used for a comparative study of nerve and muscle responses in the flexion reflex, these responses to acoustic stimuli were recorded electrically from both nerve and muscle in addition to those obtained by electrical stimulation. The latter have been shown in figures 6, 11 and 16. Figure 17 shows three responses to acoustic stimuli from the muscle and two by the usual monophasic leads from the motor nerve. In every case the stimulus consisted in a short, sharp whistle made by one of us near the animal, care being taken not to blow on the animal to avoid the confusion of a mechanical stimulus. It is interesting to note that while one response from muscle appears to indicate a simple twitch, all the others are dicrotic.

I. Reflex fatigue

The question of fatigue in the reflex arc has been discussed by Sherrington,[17] Lee and Everingham,[18] and others. One of us

[16] Forbes and Sherrington: Loc. cit.

[17] Sherrington: Op. cit., p. 218.

[18] Lee and Everingham: This journal, vol. 24, 1909, p. 384.

has shown[49] that in the flexion reflex some part of the reflex mechanism is readily fatigued, but that such fatigue does not involve the motor centre as a whole. The fatigue seems confined to the particular path of approach, presumably, according to Sherrington's view, a set of synapses.

In our experiments fatigue has been found to be strikingly manifest and rapid in its development. Records illustrating this have been secured from the majority of our preparations by operating the make and break key rapidly several times by hand while the film was running continuously at second speed (13–14 cm. per second). A record of this procedure is shown in

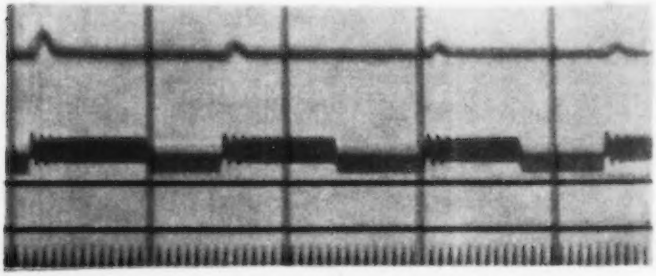


Fig. 18. Preparation 2. String C. Same tension as in fig. 5, No. 1. Stimulation from uncalibrated coil, apparently maximal. Responses from motor nerve showing reflex fatigue, see text.

figure 18. Here the coil distance was such that only break shocks were effective. In this instance it may be seen that the second response gave about half as large an excursion as the first, and the third excursion is only slightly smaller than the second; the fourth shows no further decrement. In one or two other cases slight decrement occurred between the second and third responses, but in the majority the result was such as is shown in figure 19. Here it will be seen that as in figure 18 there is a marked decrement between the first and second responses after which no further change occurs; a lower level is reached after the first

[49] Forbes: This journal, vol. 31, 1912, p. 102.

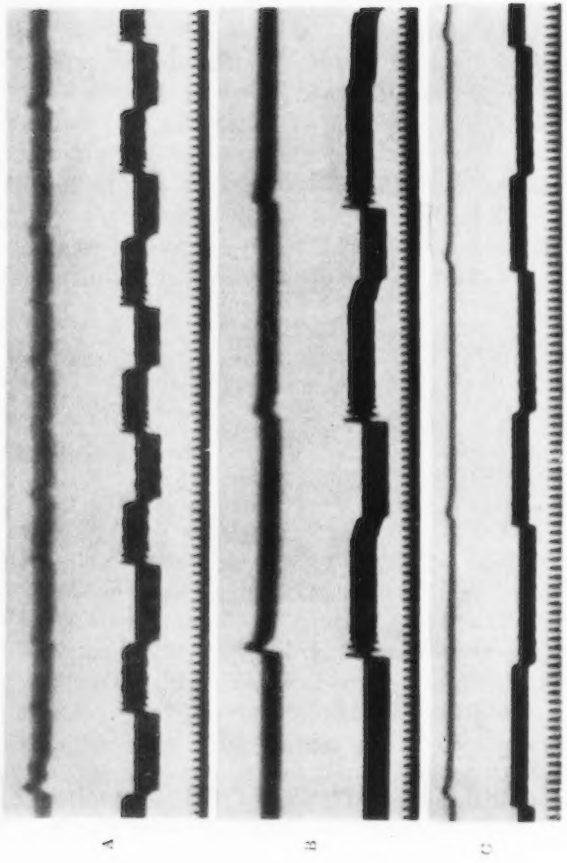


Fig. 19. Procedure as in fig. 18. *A*, Preparation 11. String *D*. Stimulation with platinum contact spring key, breaks shocks = 1560 Z. *B*, Preparation 13. String *D*. Stimulation with amalgamated copper and mercury key, break shocks = 22 Z. *C*, Preparation 29. String *E*. Stimulation with same key as in *B*, break shocks = 93 Z.

response and this remains practically constant. Figure 19, A, obtained with a simple spring platinum contact key, which could be worked very rapidly by hand, shows this approximate constancy of the fatigued response over a fairly long series. In two preparations only the first stimulus produced any clearly visible response. This condition is illustrated in figure 20.

In connection with these observations it should be noted that even when the preparation is rested the magnitude of the excursions are not always constant. Occasionally a response will be below par after the usual rest and with no apparent cause. One record obtained from the same preparation that furnished figure 19, C, shows a second response greater than the first. Here the first response was sub-normal, while the second was almost as large as one obtained just before from the preparation when

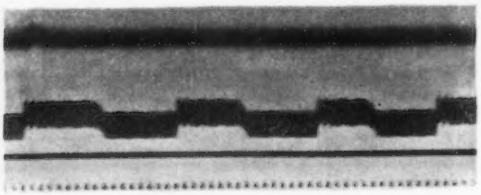


Fig. 20. Preparation 9. Apparatus and procedure as in fig. 19, A. Break shocks = 17.6 Z.

rested. The reduced size of the first response may have been caused by an accidental stimulus which may have occurred just before the observation was begun. The increased size of the second is puzzling as it stands practically alone among a large number of observations. The time interval was, however, longer than was usual between successive stimuli in these fatigue experiments and appears in this case to have sufficed for partial recovery.

In spite of this anomalous observation the uniformity of the responses following a rest of ten seconds or more was so nearly perfect and the regularity with which the results of the fatigue experiment conformed to the type shown in figure 19 was so general that we can safely accept the usual findings as valid.

The fact that the reflex arc fatigues so rapidly to a certain point and then fatigues no further during the course of the pro-

cedure employed, suggests the possibility that there are two component parts of the mechanism involved, that one part is highly susceptible to fatigue and the other highly resistant. What such component parts of the reflex mechanism might be is a matter of guess-work. If we accept the "all-or-none" view of the nerve impulse held by Adrian,[50] provided each neurone responds with a single impulse in the flexion reflex, there can be no reduction in the intensity of response in the individual motor fibres through fatigue, when the interval between stimuli is as great as in our experiments. Such reduction might occur at the synapse or in the cell body, but if a propagated disturbance passed from the latter into the axon it would, according to Adrian's view, at once attain its full intensity. This view holds that the only condition under which the impulse could continue

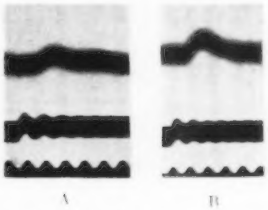


Fig. 21. Preparation 18. String *D*. Reflex responses of motor nerve. *A*, Right leg, 6 hours after decerebration, 118 *Z*. *B*, Left leg, about 24 hours after decerebration, 61 *Z*.

subnormal would be its initiation during the relative refractory period, and this in the case of the amphibian nerve at 15°C. is found by Adrian and Lucas[51] to last 0.01 to 0.02 second after the stimulus. The interval we are dealing with is often 0.25 second or more. If, then, the typical flexion reflex involves but a single impulse in each motor neurone, our observations on fatigue, to accord with the "all-or-none" view of the nerve impulse, must mean that some neurones cease to respond while others continue. If we take this view, it would further appear from our experiments that the motor neurones taking part in the flexion reflex are divided sharply in two groups, one group succumbing rapidly to fatigue, the other group continuing to respond through a long and rapid series of stimuli.

[50] Adrian: Journal of Physiology, vol. 47, 1914, p. 460.
[51] Adrian and Lucas: Loc. cit.

We do not feel that this inference can be taken as established, for the assumptions on which it rests may be open to question. We are not certain that in the normal flexion reflex each neurone responds with a single impulse, and if the response is more than that the problem is far more complicated. Furthermore, we do not feel sure that the "all-or-none" view of the nerve impulse is established beyond question, although Adrian's evidence is hard to explain on any other basis. Considering the various elements of uncertainty we cannot commit ourselves to any interpretation of the peculiar conduct of the reflex centre when subjected to fatigue.

A few records have been made of the responses of the muscle to rapidly repeated reflex stimuli. These show substantially the same features as those recorded from the nerve and possess none which make it worth while to reproduce them.

An important difference between the flexion reflex and certain other reflexes has been brought out by the experiments just described on reflex fatigue. If one watches the animal during a series of induction shocks repeated about as rapidly as was done in these experiments, the crossed extension reflex and others still more remote, such as motions of the forelimbs and trunk muscles which are usually not elicited by a single shock, exhibit a striking degree of development under summation. Whereas, on the second or third shock of such a series, the flexion reflex has fallen to a minimum, the crossed extension and other remote reflexes show at the same time a rapid increase in intensity reaching a maximum at about the fourth or fifth shock. That summation can occur in the flexion reflex has been shown in the records reproduced in figure 16. The summation time here, however, is far more brief than that which seems effective in the crossed extension reflex. Stimuli occurring within less than one-hundredth of a second of each other appear to cause summation in the flexion reflex, while stimuli a tenth of a second apart fail to do so, the second response showing a decrement in consequence of the first. Stimuli applied at the latter interval, however, produce effective summation in the case of the crossed extension reflex and others more remote. This fact serves to

emphasize still further the difference in the reflex behavior of the flexor and extensor groups of muscles already pointed out by Sherrington.[52]

J. The progressive increase in reflex activity after decerebration

One more fact in regard to the reflex behavior of these preparations remains to be noted. It is frequently found that when a series of reflex responses was recorded from the nerve over a period of an hour or more, the nerve being left intact in the moist chamber, a gradual increase in the magnitude of the excursions occurred throughout the series. This may have been due to the gradual evaporation of such excess of moisture as there may have been on the surface of the nerve, such moisture providing a path of short circuit for the action currents. That this increase may have been due also in part to a true increase in physiological activity is suggested by the following considerations.

It has already been noted that the flexion reflex was usually not obtainable for more than an hour after decerebration, and was seldom vigorous until even longer than that. It may be that this increased vigor in the flexion reflex signified more than the elimination of ether from the system. Certainly such reflexes as the postural tonus of decerebrate rigidity and other reflexes of apparently proprioceptive origin appeared after the discontinuance of anaesthesia very much more rapidly than the flexion reflex.

The view that the reflexes, and especially the flexion reflex, gain steadily in vigor for many hours after decerebration is supported by the following additional facts. In the case of several of our preparations, the animal, after being decerebrated in the morning and experimented on during the afternoon, was left over night and again experimented on the following morning. In these cases we generally found that a marked increase in the reflex responsiveness to handling and to operative procedure

[52] Sherrington: Integrative Action of the Nervous System, p. 301; Journal of Physiology, vol. 40, 1910, p. 105.

had developed during the night. In one such case the usual procedure was repeated on the second day; that is, the peroneal nerve of the other leg was led into the moist chamber and placed on electrodes for monophasic responses. In this case the obvious increase in general responsiveness was marked, but the increase in magnitude of the galvanometric excursions was scarcely less marked. Two records reproduced in figure 21 will illustrate this point. Both records were produced with maximal stimulation. The first record (A) was taken in the afternoon of the first day about six hours after decerebration; the second (B) was taken the following morning in the neighborhood of twenty-four hours after decerebration. We are not prepared to state that such an increase in activity is universal, but from the few observations we have made on this point it does appear to be general.

SUMMARY

1. An optical system is described whereby the light of a Nernst lamp can be sufficiently intensified to make possible the taking of string galvanometer records with a magnification of 550 or 600 diameters and with a velocity of the photographic film amounting to 30 or 40 cm. per second, the definition sufficing for observations having a fair degree of accuracy.

2. A recording camera is described wherewith large numbers of observations can be photographically recorded in rapid succession without any requisite adjustments between. Taken in connection with the optical system, it provides an extremely convenient and elastic outfit for physiological use of the string galvanometer, involving a minimum of distraction from the purely physiological features of experimentation.

3. With the above apparatus, supplemented by illumination with an arc lamp in a few experiments when accurate time measurements were desired, the flexion reflex was examined in the decerebrate cat by stimulating an afferent nerve in the hind leg with single induction shocks, and recording the action currents in the flexor muscle (tibialis anticus) and in its motor nerve.

4. Typical monophasic nerve action currents induced by reflex stimulation are recorded and compared with monophasic responses in the same nerve to direct stimulation.

5. A large number of such records show an observed time elapsing between stimulus and response ranging from 7.7σ to 12.8σ. From these measurements it is estimated that the "reduced reflex time" normally lies between 3 and 5σ.

6. The reflex responses in nerve to maximal stimulation are much smaller and less abrupt in their onset than the responses to direct stimulation, i.e., the electrical disturbance increases to a maximum more gradually.

7. When the nerve is giving typical reflex responses no additional information in regard to their interpretation is afforded by the diphasic method. One preparation, giving exceptionally small and short responses, furnished diphasic responses indicating that the motor impulses in the individual fibres are essentially the same, at least as regards time relations, in the case of reflex as in the case of direct stimulation. From this it is argued that the gradual onset of the typical monophasic reflex response signifies unequal latency in the individual reflex arcs, and not a qualitative difference in the individual impulses.

8. Occasionally a preparation is found in which the motor nerve with monophasic leads responds to the usual reflex stimulus with a dicrotic or double action current. This does not necessarily mean that any neurones discharge twice; it may be readily explained as a double grouping of the reflex times in the many individual arcs.

9. When the galvanometer is connected directly with the substance of the flexor muscle instead of its motor nerve, responses to reflex stimuli are obtained which differ from those obtained from the nerve in the following respects; the excursions of the string are larger, and they lack the uniformity of the nerve responses, being far more variable in shape and magnitude and often changing from single to double or double to single within a few minutes. Whether this signifies double response in some of the muscle fibres or rapid change of latency in some of the nerve-muscle units, it shows that muscular action currents

must be used with caution as an indicator of central nervous rhythm.

10. Great augmentation of magnitude in the reflex muscular response is found under rapid summation of afferent impulses. This is not so evident in the nerve response. It is notable that the summation time is much briefer in the flexion reflex than in the crossed extension reflex.

11. In one preparation action currents were led off from both the flexor muscle and its motor nerve in response to acoustic stimuli. This reaction is very unusual.

12. The flexion reflex as recorded in the action current of the motor nerve is subject to very rapid fatigue. After the first of a series of stimuli, the response usually falls to a reduced magnitude at which it remains without further reduction. It is suggested that there are two component parts of the reflex mechanism, one part highly susceptible, the other highly resistant to fatigue. The same series of stimuli which develops flexor fatigue simultaneously produces extensor augmentation through central summation.

13. It is common to find a slow progressive increase in the vigor of the reflex responses for many hours after decerebration, and continuing until the following day.